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MYELOGENOUS LEUKEMIA INDUCED IN RATS WITH CHRONIC MAGNESIUM DEFICIENCY

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INTRODUCTION

Leukemia occurs in several species as a spontaneous disease of undetermined etiology. It may also be induced by viruses, chemical carcinogens and ionizing radiation. Poultry and mice of certain strains are particularly susceptible to the disease while rats are relatively resistant. Rats of various strains are particularly resistant to subacute or chronic myelocytic leukemia, at times designated as chloroleukemia. As shown in Table I, this disease has seldom been encountered as a spontaneous disorder.[1–6] Except for one report concerned with the occurrence of myelocytic leukemia with an incidence of 3.0 per cent in a colony of very old rats, the incidence may be regarded as nearly negligible.[1] It has been possible to induce the disease by dietary methylcholanthrene.[7–9] When dietary methylcholanthrene was combined with x-irradiation, the disease occurred with somewhat greater frequency.[10,11] A similar incidence was encountered among rats fed acetylaminofluorene for many months, especially when the animals had been on an ethionine dietary regime or had received sufficient carbon tetrachloride to produce prior hepatocellular degeneration.[12,13] The chemical carcinogen, 2-acetylaminophenanthrene, proved to be strongly leukemogenic, but the type of leukemia was not easily defined in most instances.[14,15] Myelocytic leukemia has been reported in only one animal among many groups of rats fed the hepatic carcinogen, butter yellow, or one animal among many groups of rats in which the skin has been painted with benzpyrene dissolved in benzene.[16,17] Oral administration of the radioactive element, actinium 227, also was essentially ineffective in producing the disease.[18] Results by use of a high fat diet, usually combined with DDT, were more impressive, but the incidence of the disease was only about 5 per cent in the Osborne-Mendel strain which seems to have a rather high spontaneous incidence.[1,2,19] A high incidence was reported in a small group of rats given multiple injections of a cell-free filtrate of

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a rat tumor.[20] Of considerable interest was the occurrence of the disease in the offspring of rats fed 4-aminopteroyl glutamic acid.[21]

The reports listed in Table I are all which we have been able to find in which a description has been made of the spontaneous or induced incidence of subacute or chronic myelocytic leukemia in the rat.

In no instance has there been any relation established between any nutritional deficiency and the pathogenesis of the disease, though several deficiency states in man may have hemotologic manifestations of a leukemoid nature. This report presents evidence which indicates that chronic magnesium deficiency in the rat favors the occurrence of a disease which is indistinguishable from chronic myelo-

TABLE I

Spontaneous and Induced Myelocytic Leukemia in the Rat

Reference	Method of Production of Leukemia	Strain	Number in Study	Number with Leukemia	Percent with Leukemia
1	Spontaneous	Osborne-Mendel	365	11	3.0
2	Spontaneous	Osborne-Mendel	498	6	1.2
3	Spontaneous	—	—	1	—
4	Spontaneous	—	6000	3	0.05
5	Spontaneous	—	500	1	0.20
6	Spontaneous	—	—	3	—
7	Oral methyl cholanthrene	Wistar	800	3	0.375
8	Oral methyl cholanthrene	—	—	9	—
9	Oral methyl cholanthrene with thyroidectomy	Fischer	10	1	10.0
10	Oral methyl cholanthrene with x-irradiation	—	20	2	10.0
11	Oral methyl cholanthrene with x-irradiation	Wistar	303	9	2.97
12	Oral 2-acetylamino-fluorene	Wistar	84	2	2.4
13	Oral 2-acetylamino-fluorene				
	Ethionine-carbon tetrachloride	Wistar	85	4	4.7
14	Oral 2-acetylamino-phenanthrene	—	74	12	16.2
15	Oral 2-acetylamino-phenanthrene	Holtzmann	117	56*	48.0*
16	Oral O-amino azotoluene with methylene blue	—	20	1	5.0
17	Cutaneous benzene-benzypyrene	—	15	1	6.6
18	Oral actinium 227	Sprague-Dawley	100's	2	—
19	High fat diet with DDT	Osborne-Mendel	135	7	5.2
20	Injections for cancer filtrate	Wistar	10	3	30.0
21	Oral 4-amino pteroyl-glutamic acid			4**	

*Mostly lymphocytic or indefinable leukemia. One was chronic granulocytic leukemia.

**Leukemia appeared in fourth and fifth generations.

cytic leukemia as ordinarily defined in this species.

METHODS

Charles River (CD) male rats derived originally from the Sprague-Dawley strain were used. At the beginning of the experiment they were about 8 weeks old and weighed 100 to 140 grams. They were individually housed in metal cages in the same environment as the control animals. They had free access to distilled water and their respective diets. All animals were weighed weekly and a record kept of their clinical status. Complete autopsies were done in all instances whether the animals died spontaneously or were sacrificed. Blocks of tissue from all organs were fixed in formalin and sections prepared for microscopic study by routine histologic methods. White blood cell counts and differential counts of nucleated cells in blood smears were done on some animals terminally. Magnesium determinations were made of each newly prepared diet prior to its use. Serum magnesium determinations were done in selected cases as a guide to the assessment of the effectiveness of the diets in establishing a state of magnesium deficiency. All magnesium determinations were made in duplicate on serum and samples of diet by use of a Model 214 Perkin-Elmer atomic absorption spectrophotometer.

Animals were divided into four groups as follows:

Group I consisted of 8 rats placed on a synthetic diet which, prior to supplementation, contained less than 1 mgm. of magnesium per 100 grams[22]. When fed to the animals it was supplemented with sufficient $MgCl_2$ (C.P.) to bring the concentration of magnesium to an average level between 5 and 6 mgm. per 100 grams of diet. The rats were maintained on this diet for 6–12 months.

Group II consisted of 20 rats fed the same synthetic diet as Group I, except that it was supplemented with sufficient $MgCl_2$ (C.P.) to bring the average concentration of magnesium to about 65 milligrams per 100 grams of diet. This amount of magnesium is regarded as sufficient to support normal growth and development. This control series of rats was maintained for more than 12 months on the diet.

Group III consisted of 12 rats fed the synthetic diet which contained 5–6 milligrams of magnesium and 60 milligrams of 2-acetylaminofluorene (2-AAF) per 100 grams of diet. These animals were studied more carefully than those in Group I, which was essentially a pilot experiment. Blood leukocyte counts and differential nucleated cell counts of peripheral blood were made prior to death in 9 of the 12 rats.

Group IV consisted of 194 rats fed the basal synthetic diet supplemented with 65 mgm. of magnesium and 60 mgm. of acetylaminofluorene per 100 grams. This control series was kept on the regime for 6–18 months.

In summary, therefore, the entire experiment consisted of two groups of animals on a chronic magnesium deficient dietary regime with one of the two groups also receiving a weakly leukemogenic but strongly carcinogenic chemical compound, 2-AAF[12,13]. Each experimental magnesium deficient group was paired with a control group fed comparable diets but with an adequate supplement of magnesium and maintained for an equal or longer period of time before termination of the experiment.

RESULTS

The 8 rats in Group I periodically exhibited cutaneous hyperemia and increased irritability. This sign and symptom, characteristic of rats with acute severe magnesium deficiency, were interpreted as an indication of the probability that the chronic deficiency was nearly maximal. This was especially so in the younger animals for, with increased duration of the experiment, the older animals seemed to have less requirement for magnesium. The magnesium deficient animals, as a group, gained weight at a slower rate than the control animals of

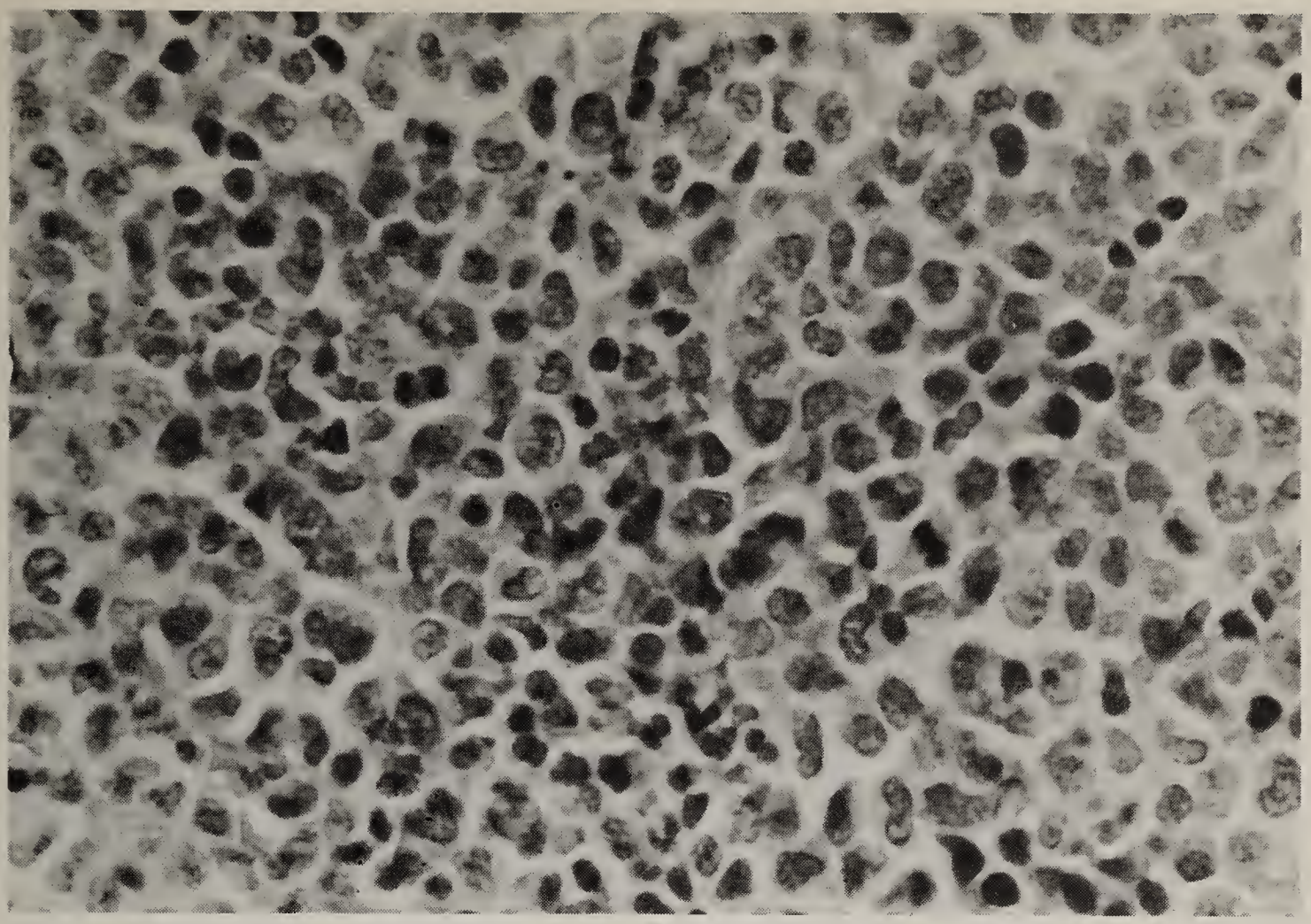

Fig. 1.—This is a photomicrograph of the bone marrow of a leukemic rat in Group I. The bone marrow here and elsewhere was composed almost entirely of closely packed immature myeloid cells, some of which are in mitotic division. X600

Group II, but after several months there was little important difference between animals in Group I and Group II.

Two of the 8 rats in Group I developed myelocytic leukemia. There was no evidence of leukemia among the 20 rats in the control series, Group II. The first rat with recognized leukemia had marked cutaneous pallor prior to death which occurred at the beginning of the sixth month on the diet. At this time the blood had a milky appearance. There was, at autopsy, a massive enlargement of the spleen and greenish gray cellular infiltrates were present in the bone marrow, lymph nodes and several organs. In these locations, microscopic studies disclosed a massive infiltration with immature myeloid cells. This was particularly impressive in the spleen, liver and bone marrow. (Fig. 1,2,3,4,5) The degree of activity in the bone marrow was such that the immature cells frequently extended outside of the bone into the regional muscle and other supporting tissues. (Fig. 2,3)

The second rat in Group I with leukemia lived for ten months and, after a clinical course similar to that of the leukemic rat described above, died with essentially identical gross and microscopic changes, diagnosed as subacute or chronic myelocytic leukemia with widespread involvement of most tissues and major organs.

The remaining 6 animals of Group I were sacrificed at the end of 12 months on the magnesium deficient dietary regime. All had myeloid hyperplasia in

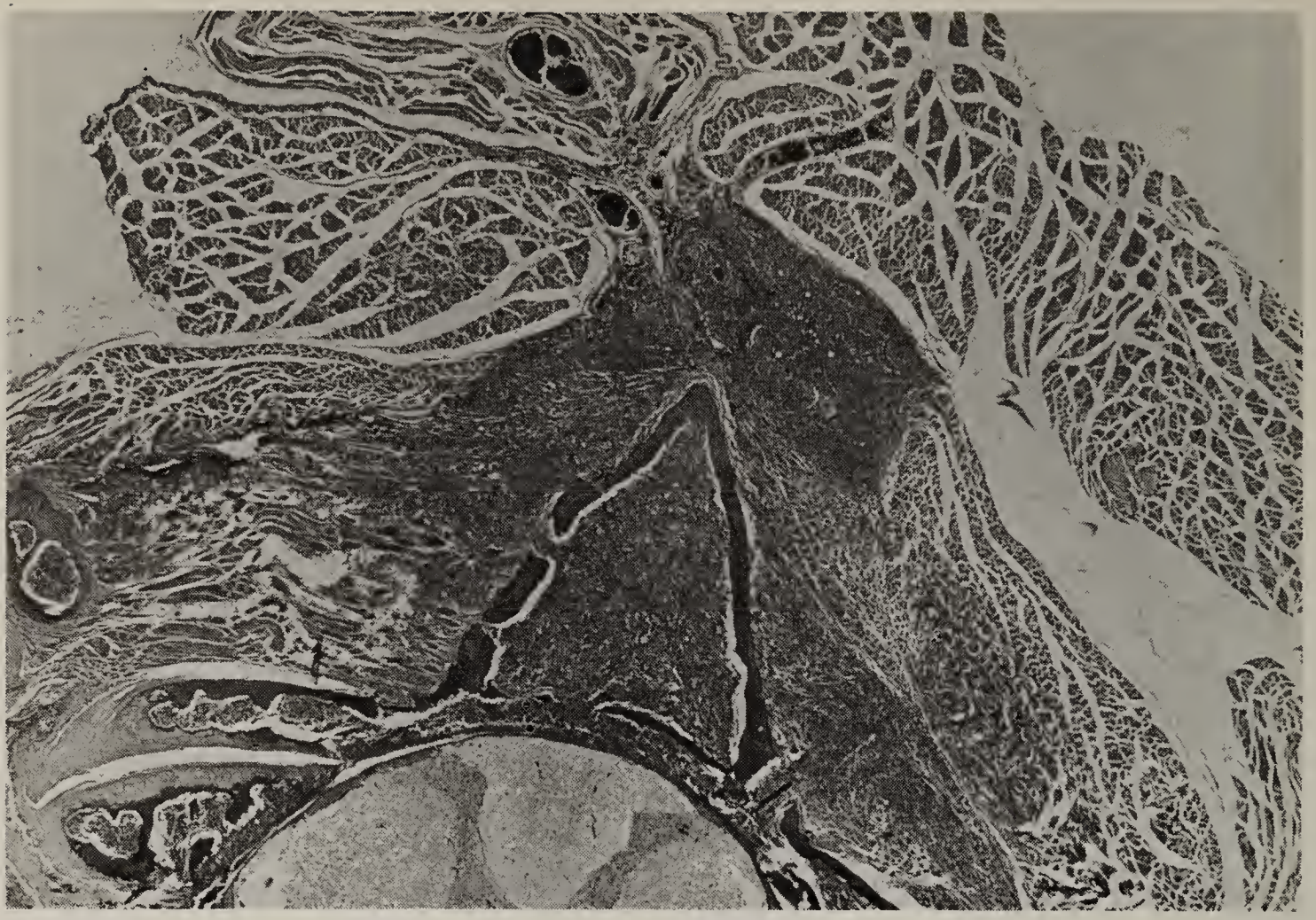

Fig. 2.—This is a photomicrograph of a transverse section of a vertebra and adjacent structures, including a portion of the spinal cord and paravertebral muscle. The bony spinous process is filled in its marrow space with a compact mass of myeloid cells which have spread widely from the confines of the marrow space into the regional skeletal muscle and epidural space. The specimen was obtained from a leukemic rat of Group I. The cells in the marrow and adjacent tissues are of the same type as those shown in Figure 1. X25

the bone marrow and to a lesser extent in the spleen, but there was no evidence of leukemia in the blood or other tissues. All had, to a variable degree, the usual cardiac, skeletal muscle and renal lesions characteristic of chronic magnesium deficiency in the rat. These pathologic changes were, in general, no less severe than corresponding changes encountered in the two magnesium deficient rats which developed leukemia.

Although leucocytic counts and differential smears were done only terminally on 9 of the 12 animals in Group III, comparable animals in an experiment now under way are being serially counted. In all animals, the control levels pre-experimentally are between 8,000 and 12,000 leucocytes per mm.^{3} of blood with an average of 20 per cent mature granulocytes in the differential counts. During the period of Mg deficiency and 2-AAF supplementation, the blood counts fluctuate, but as a rule range from 20,000 to 50,000 per mm.^{3}. The percentage of mature granulocytes also fluctuate but do not approach the levels of 50-90 per cent encountered in the leukemic animals of Group III.

Four of the 12 rats of Group III developed subacute or chronic myelocytic leukemia as defined by a combination of hematologic studies during life and postmortem histologic studies. Only 3 of 194 control rats in Group IV had leukemia as determined by complete postmortem histologic studies, for in this large group routine serial hematologic studies were

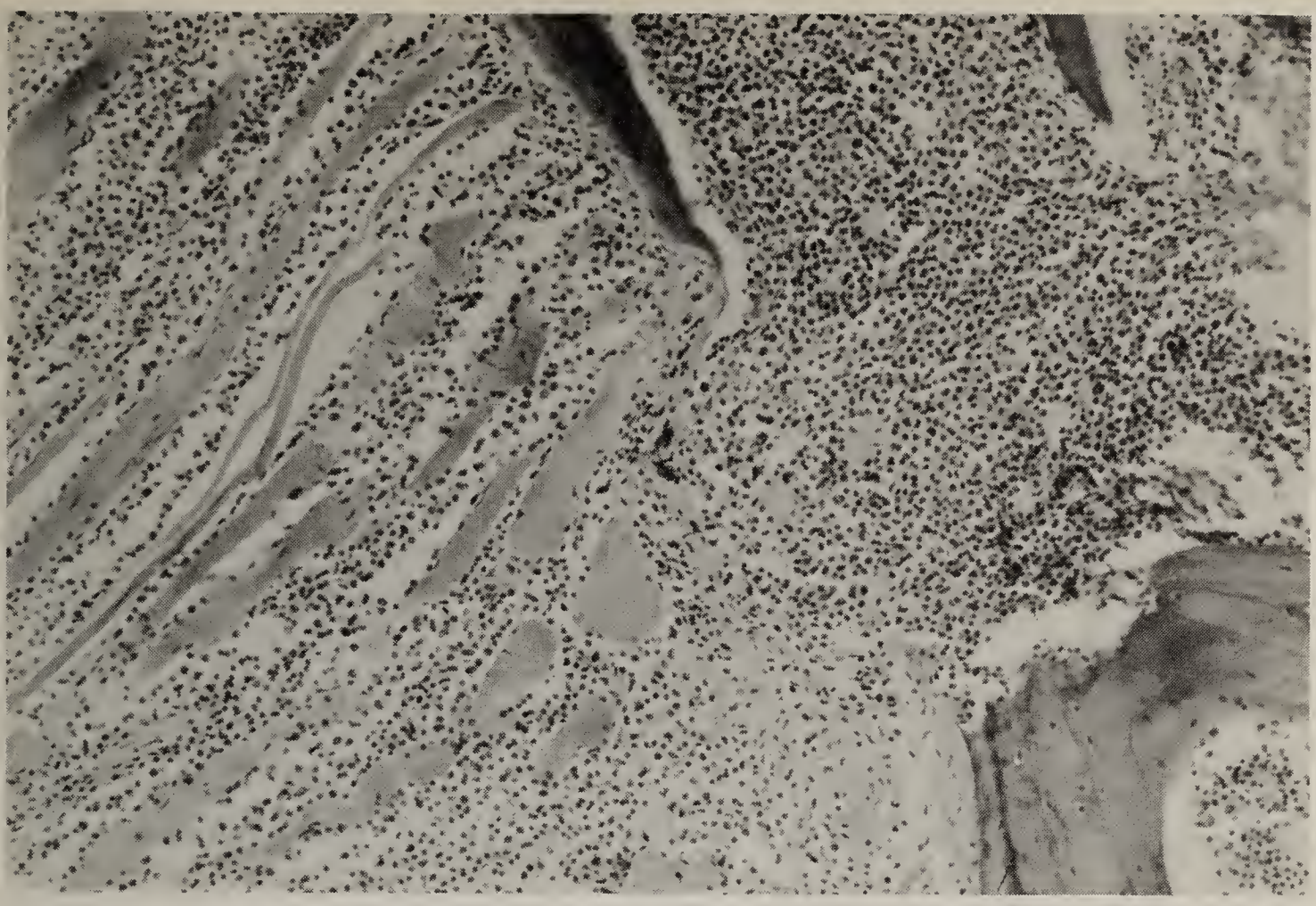

Fig. 3.—This is a photomicrograph of a portion of the spinous process and adjacent skeletal muscle illustrated in Figure 2. Note the erosion of the cortical bone by the massive proliferation of myeloid cells in the marrow and the spread of these cells through the defect into the adjacent extraosseous mass of attached muscle cells. X125

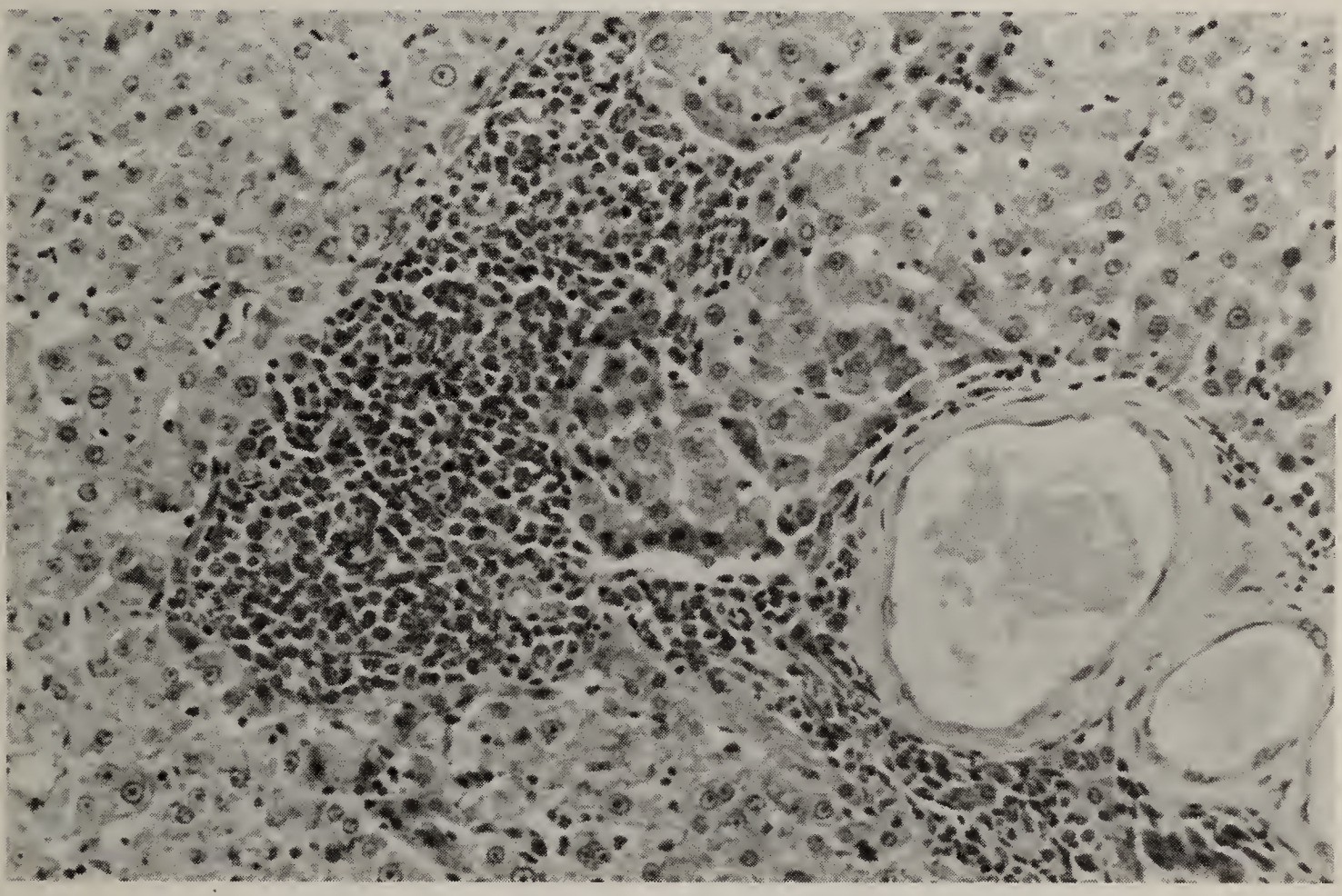

Fig. 4.—This is a photomicrograph of a paraffin section of the liver of a leukemic rat of Group III. This is representative of an area of moderate infiltration with immature cells of the myeloid series as noted in all animals of Groups I, III and IV with chronic myelocytic leukemia. X350

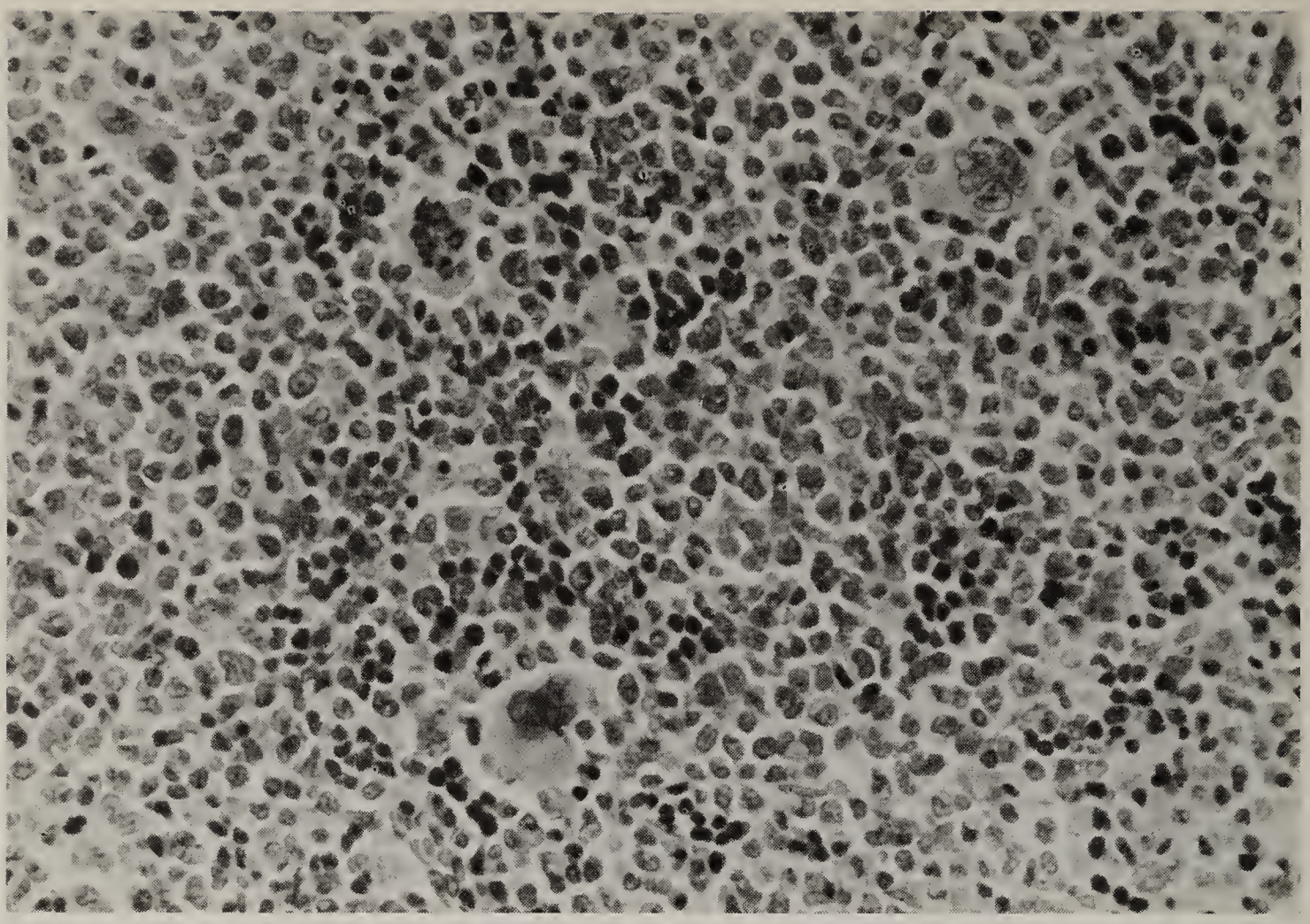

Fig. 5.—This photomicrograph is of a paraffin section of the spleen of a leukemic rat in Group III. As was the rule in all cases of leukemia, there was, as shown here, almost complete replacement of the pulp of greatly enlarged spleen by masses of immature myeloid cells with a few interspersed megakaryocytes and lymphocytes. X500

not done during life. Two of the 4 leukemic rats in Group III had blood leukocyte counts fluctuating between 60,000 and 120,000 per mm.^{3} with occasional "blasts" in peripheral blood smears. Both died at the end of 8 months on the diet. The third and fourth leukemic rats died during the ninth month with blood leukocyte counts of about 20,000 per mm.^{3} Differential smears of the peripheral blood in one case showed mostly mature granulocytes while in the other animal there were numerous "blasts" and immature myeloid cells. Microscopic study of tissues obtained at autopsy showed changes in 2 cases which were essentially identical with those described in the leukemic animals of Group I. (Fig. 4,5) In the third and fourth leukemic rats of Group III the structure of the spleen and bone marrow was replaced by immature myeloid cells, but there was less conspicuous infiltration of other organs and tissues. Among the remaining 8 animals of Group III, all of which lived for 8–12 months, there was myeloid hyperplasia in the bone marrow, but no definitive microscopic evidence of leukemic infiltration of organs of tissues. These animals, as well as those with leukemia, had not only a variable depression in the serum magnesium levels, but also changes in cardiac muscle, skeletal muscle and kidney attributable to magnesium deficiency (23,24). Neither the magnitude of these changes nor the absolute level of leukocytosis was consistently related to the occurrence of leukemia.

Among the 194 control animals in Group IV, there were 3 cases of leukemia. These had essentially the same characteristic features as the leukemic animals in Groups I and III. In addition, however, as was the case in all animals of Group III, there was in Group IV the expected high incidence of neoplasms, especially of the liver, urinary bladder and acoustic duct attributable to ingestion of 2-AAF[12,13]. There was no correlation between the occurrence of one or more of these tumors and the development of leukemia in Groups III and IV.

DISCUSSION

The extensive literature concerned with magnesium deficiency in the rat and several other species has recently been reviewed[23,24]. The only observation which seems to bear directly on the present study was made during a study of the blood leukocytes in rats, acutely deficient in magnesium[25,26]. In the first of the two reports it was shown that young male Wistar rats developed a conspicuous leukocytosis and an eosinophilia which reached a maximum by the 8th day of the deficiency and returned toward control levels by the 15th day[25]. In a subsequent report, young male Holtzman rats with acute magnesium deficiency had a blood and tissue eosinophilia which declined toward normal values as the deficiency was prolonged to 6 weeks. A massive infiltration of eosinophiles into lungs, salivary glands, and mesenteric lymph nodes was noted in all magnesium deficient groups. No mention of the relations between the increase in blood or tissue eosinophiles and the total blood leukocyte count was made[26].

In our experiments with acute magnesium deficiency, which have not yet been reported in detail, we have confirmed the rise and subsequent fall of the total blood leukocyte count, but not the occurrence of much more than a proportionate elevation in the total circulating blood eosinophile count. The rise of the total leukocyte count could theoretically be attributed to a reaction of the leukopoietic system to the pathological changes in tissues, characteristic of magnesium deficiency[23,24]. However, close examination failed to disclose a consistent relation between the magnitude of pathologic changes at autopsy and the degree of leukocytosis during life of the acutely magnesium deficient animals. Inasmuch as it was difficult to maintain rats beyond 6 weeks on a diet highly deficient in magnesium (less than 1 mgm.% of magnesium), it was decided that further inquiry into the pathogenesis of the leukocytosis should be made by use of a limiting chronic magnesium deficiency dietary regime. It was soon found that rats would grow and could be maintained in a fair state of health and nutrition if the diet contained about 5 milligrams of magnesium per 100 grams during the first few weeks. As the rats grew older, it was possible to reduce the dietary magnesium content to lower levels, thereby maintaining a state of maximal chronic deficiency compatible with prolonged life. By this means whatever accommodation the animal might make to the deficiency was compensated for by the judicial further dietary reduction in magnesium supply. By recourse to this technique it was usually possible to overcome the natural tendency of the elevated blood leukocyte count to return toward normal levels and to create conditions which favored persistence of a fluctuating blood leukocyte count at a high level. With the maintenance of a state of chronic leukocytosis, smears of the peripheral blood gave little support to a definitive diagnosis of leukemia. The leukocytes were principally mature with only a few immature myeloid cells and rare "blasts." Hence, it was a surprise when 2 of 8 animals in this initial pilot experiment showed, at autopsy, a profound infiltration of immature myeloid cells throughout many organs and tissues.

Our first reaction to this most unusual finding was to try to increase the incidence of leukemia by combining a weakly leukemogenic chemical compound, 2-AAF, with chronic magnesium deficiency. The combination of the chem-

ical carcinogen with the small amount of magnesium in the diet resulted in development of chronic myelocytic leukemia in 4 of 12 rats. Meanwhile, among 194 rats maintained on a diet containing adequate amounts of magnesium and the same quantity of 2-AAF as the experimental group, only 3 developed chronic myelocytic leukemia. Among many other animals of this strain which we kept on normal diets for 8–12 months, none have developed chronic myelocytic leukemia, so that the natural incidence of this disease in this strain of rats is very small indeed. This would also seem to be true of other strains of rats as indicated in Table I and in reviews of the literature[27-30].

One may speculate at length about possible mechanisms responsible for the consistent myeloid hyperplasia in the bone marrow, the neutrophilic leukocytosis and the possible eosinophilic leukocytosis characteristic of acute magnesium deficiency in the young rat. It became increasingly important that insight into these mechanisms be gained when it was apparent that the myeloid hyperplasia and persistent increase in the number of blood leukocytes of the myeloid series could be maintained by prolongation of the acute deficiency into a state of stable chronic magnesium deficiency. It has now become still more important to inquire further into the subject in view of the evidence that the prolonged myeloid hyperplasia and blood leukocytosis favor the mergence of the process into a pathologic state which can at the moment only be defined as a chronic myelocytic leukemia of undetermined cause.

SUMMARY

Young male Charles River (CD) rats were placed on two dietary regimes. One regime was composed of a synthetic diet containing no more than 6 mgm. % of magnesium. This diet was supplemented with 0.06% 2-acetylaminofluorene as the basis for the second regime. Eight animals on the first regime and 12 animals on the second regime were maintained for 6–12 months in a state of chronic magnesium deficiency. All animals at autopsy had myeloid hyperplasia of the bone marrow and the characteristic pathologic changes of magnesium deficiency in the myocardium, skeletal muscle and kidney. Two of 8 rats on the first regime and 4 of 12 rats on the second regime also had severe disseminated infiltrative myelocytic leukemia. Nine of 12 rats on the second regime had high leukocyte counts terminally and of the 4 with leukemia the counts ranged from 50,000 to 120,000 per mm.^{3} with differential smears compatible with a diagnosis of chronic myelocytic leukemia. Spontaneous leukemia has not been reported in this strain of Sprague-Dawley rats. There was no evidence of leukemia in 20 animals carried as controls for those on the first regime. As a control for the second regime, there were only 3 leukemic rats out of 194 animals given a weakly leukemogenic chemical compound, 2-AAF, in combination with a diet adequately supplied with magnesium. The mechanisms responsible for the leukocytosis of acute magnesium deficiency, the persistence of the leukocytosis and accentuation of myeloid hyperplasia in the bone marrow with prolongation of the deficiency for several months and eventual development of a subacute or chronic myelocytic leukemia are obscure.

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FROSTBITE

Geza de Takats, M.D.

INTRODUCTION

The problem of cold injury confronts the physician comparatively rarely in our climate. Only large, municipal hospitals during unusùally heavy winter weather receive enough frostbitten patients to develop some material. It is all the more important that other sources of experience, namely, that of the Armed Services, of the Arctic explorers and of high altitude mountain climbers, be examined, since poor prevention and early inadequate treatment have demonstrably dire results.

According to the Farmer's Almanac, we are in for a warm fall and a heavy winter this year. In addition, the number of outdoor workers in higher age groups is considerable. Pre-existing vascular disease greatly aggravates the effect of cold on the extremities, or other exposed parts of the body. The fact that a middle-aged street cleaner with a temperature of +20° Fahrenheit and a 45 mile wind, suffers severe damage to his toes, always confounds the claim agent, who is unaware that the chilling effect of this combination is equivalent to that of a –40° Fahrenheit temperature with a 2 mile per hour breeze, and that the man has demonstrable arterial disease.

Based on experience in the First World War in the field, in the Second World War in Army and Navy hospitals, and during participation in follow-up studies on veterans with cold injuries[1], certain principles have been formulated which will be briefly discussed. Particular emphasis will be given to rapid thawing, since this method, extensively studied experimentally by Shumacker and Lempke[2] has now received adequate confirmation by experience in Alaska.[3]

TYPES OF COLD INJURY

Cold Allergy. Urticaria develops on portions of the body directly exposed to cold air, water or a chip of ice (Fig. 1), but there may be a generalized reaction, angioneurotic edema, fall in blood pressure and rise in pulse rate. A number of unexplained drownings may be due to such sensitivity to cold and one of the most talented and popular surgeons has been said to have drowned this way. This peculiar reaction is rare, and has no bearing on cold injuries; in fact, such a reaction warns and protects the individual from continued exposure. Eating ice cream or drinking ice-cold beverages can bring on a histamine-like response.

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Chilblains. Acute chilblains predominantly affect the hands, feet and legs of bobby-soxers, many of whom wear thin hose or no hose at all, are anemic or hypometabolic. Acute chilblains are the earliest state of a localized frostbite. More recently, we have seen them under hypothermic anesthesia. Chronic chilblains occur on repeated exposure. Poliomyelitic and obese, lipedematous legs are prone to develop large, purplish, sometimes itching indurations, often mislabeled as erythema induratum and suspected to be of tuberculous origin. Often called pernio, chilblain is a vascular disease, shows fat necrosis, giant cells, periarterial reactions indicating increased vascular permeability. Fat dissolution is prominent (Fig. 2).

Fig. 1.—Chip of ice placed on sternum of D.R. 335-725, 12-1-47, University of Illinois. This 22 year old, anemic girl was also allergic to sunlight.

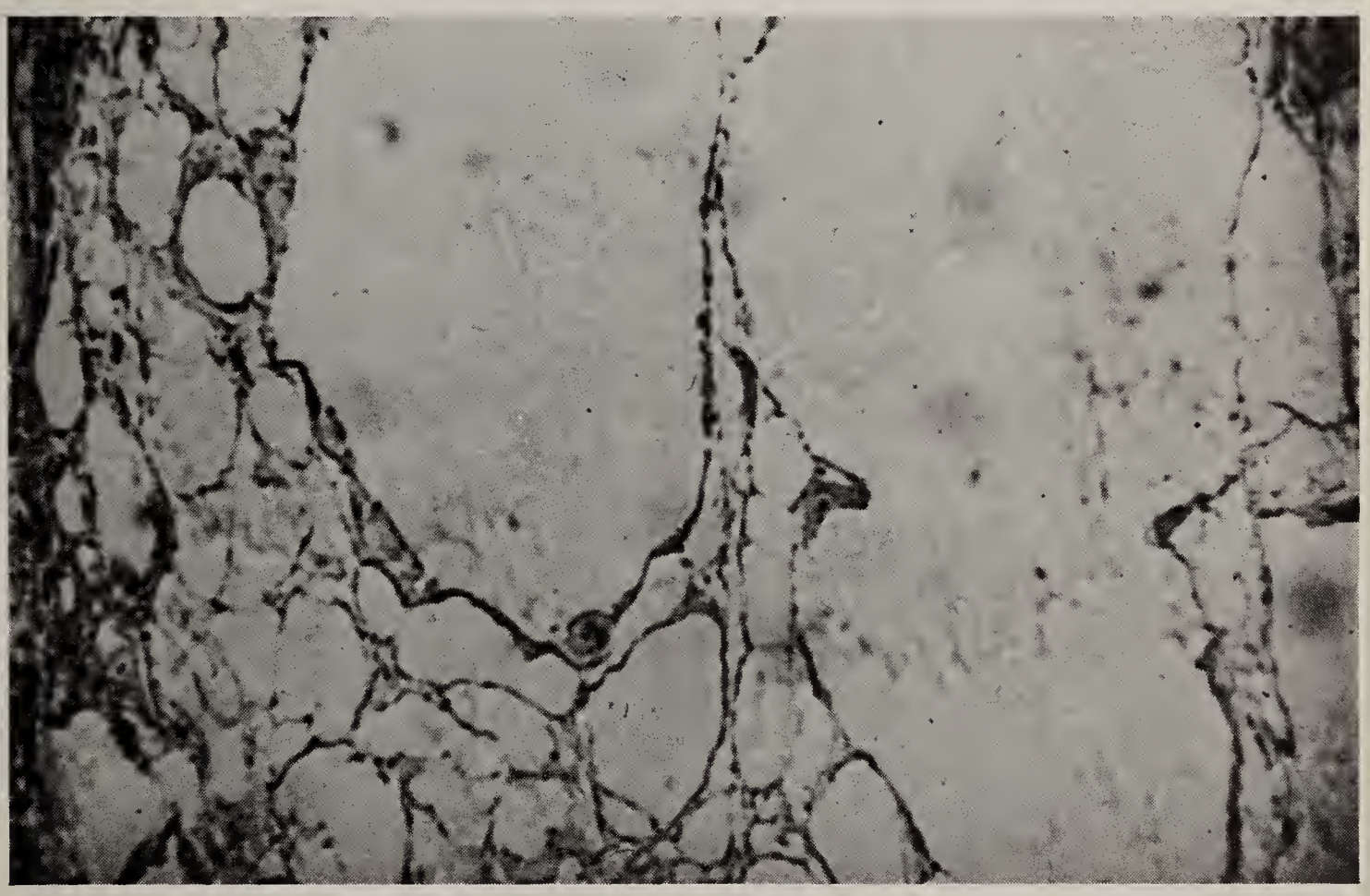

Fig. 2.—A purplish, painful induration in a poliomyelitic limb, excised following a lumbar sympathectomy. Note the fat necrosis, scarring and cuffing of small arteries. This 34 year old patient showed no other evidence of vascular disease. From de Takats, G., Vascular Surgery, W. B. Saunders Company, Philadelphia and London, 1959.

Immersion Limb or Trench Foot. These are similar, if not identical conditions resulting from a chronic exposure to mild, slightly above freezing temperatures, dampness, constriction of garments, immobility, hunger, pain and panic. While records of trench foot go back to the earliest times, in the early months of World War II the terms "waterbite", "life-boat leg" and "sea-boot foot" were described. Immersion limb has been described in Royal Air Force personnel who spent many hours on exposed Scottish moors after airplane crashes[4]. The temperature does not have to drop below freezing, but dampness and windchill are prominent.

Frostbite. Strictly speaking, frostbite occurs when tissue is frozen; however, a first degree frostbite which consists of a white, insensitive patch of skin without blistering or peeling, is certainly completely reversible. As Washburn[5] points out, however, there is little merit in classifying frostbite into four degrees. In the first place, the degree of frostbite can not be ascertained immediately after exposure. And secondly, the treatment for all degrees of frostbite is identical and an initial diagnosis of degree seems of little practical value.

It is therefore best to classify frostbite into two types; superficial and deep. **Superficial frostbite** involves only the skin which is white and frozen, but soft and resilient below the surface when depressed gently. The skin may blister later, or even dry up and form a gangrenous patch in about two weeks, but the patch will fall off leaving a red, tender skin, sensitive to cold. This area may perspire abnormally for a long time.

Deep frostbite involves not only the skin and subcutaneous tissue, but extends deep into muscle and even bone. Blisters develop much more slowly. Marked swelling, limitation of motion and blue, violet or gray discoloration take place. Demarcation of dead tissue is slow, may take weeks or months, and autoamputation of fingers and toes occur. If infection is not prevented, wet gangrene develops with swelling and ascending lymphangitis.

FUNCTIONAL PATHOLOGY[6]

Man's sensitivity contrasts greatly with the resistance to cold of hibernating or arctic animals. The white fox sleeps on snow or at atmospheric temperatures as low as —50°C. without experiencing frostbite or even shivering. Pigeons seen in the Arctic survive for 144 hours at —40°C., but die within 20 minutes if exposed to the same temperature after their feathers were plucked. Insulation and high metabolic rate of birds, however, are not the only factors involved. The legs and feet of Arctic mammals endure long periods of temperatures which would be harmful to human tissues. Nevertheless, adaptation or tolerance to cold develops in humans too. Baltic porters, for example, can walk **barefoot** for hours through the Himalayan snow carrying heavy loads at 13,000 to 16,000 feet without visible injury or discomfort[5].

Cold acclimatization and adaptation have been carefully studied by a number of investigators[7]. Unless sufficiently dressed, indoctrinated and alerted, the average Sunday hunter, used to overheated houses and offices, will be more readily frostbitten than the hardy, tough, weatherbeaten faces, hands and feet of Eskimos, Tibetans and other natives in cold, rugged climates.

In man, severe vasoconstriction occurs as a local and direct effect of cold on microvasculature. Capillary blood then slows down and may come to a complete standstill partly because of lack of propulsive pressure, but also because of red cell agglutination. Thirdly, reflex, neurogenic vasoconstriction occurs, mediated partly by painful impulses, but also by the chilled blood affecting the heat regulating centers. This triad of vascular response institutes a vicious circle and if not broken, quickly will lead to permanent damage, freezing of tissue with the formation of crystals and rupture of cells on thawing. This may occur as a direct cold injury to cells without any vascular component.

Coincident with capillary stasis, capillary permeability increases, protein rich edema exudes into the tissues and a sterile

inflammation is set up. Even if the extremity escapes gangrene, it will show periarterial and perineural fibrosis, fat necrosis and gradual atrophy. The small, non-medullated vasomotor fibers remain more intact than some of the medullated somatic fibers. Numbness, tingling, burning and excessive sweating remain for a long time. I have seen it persist in frostbitten toes for as long as 40 years.

Profound hypothermia with an irregular pulse of 20 per minute and a respiratory rate of 3–5 a minute, firm, rubbery skin over the entire body and a rectal temperature 18° C. (64.4 F) was observed in a patient found unconscious in the snow. Outdoor temperatures varied from −11° F. to −15° F. A complete physiologic study of her recovery rate was published by Laufman.[8] Though she lost both legs and most fingers, she made a remarkable recovery. She was rewarmed slowly, her body temperature returning to normal in about 20 hours. Since that time, many patients have been subjected to transient deep hypothermia during cardiac surgery. Abundant physiologic observations during hypothermia and on rewarming are available.[9]

PROPHYLAXIS

Again, the experience of the Armed Forces, the hunters, explorers and Eskimos need to be carefully examined. Maintenance of general body warmth by adequate loose, warm, dry socks, which require frequent inspection and change are important. Perspiration should be avoided under conditions of extreme cold. All types of boots must be used with great care during periods of inactivity, after exercise has resulted in damp socks or insoles. The importance of the "buddy-system" was forcibly brought home during the Battle of the Bulge. Two divisions were side to side, the one with more up-to-date footwear suffering a higher percentage of cold injuries compared with the other one, where frequent inspection of the feet and relief from front duty in extreme cold were observed.

Mittens should be worn instead of gloves in extreme cold, unless manual dexterity is required for short periods as in photography or surveying. For these periods, silk or rayon gloves can be used. Metal objects should never be touched with bare hands, particularly when the hands are moist.

Men who have seen war service during extreme cold conditions may smile wryly at these suggestions—but good indoctrination and understanding of what to avoid may save limbs. Many of the men are injured, hypotensive and can not be moved; fear, pain and panic increase perspiration; high altitude anoxia greatly adds to the damage.

TREATMENT

There are three phases of cold injury—the acute one requiring immediate treatment; a subacute phase in which necrosis or return to viability is apparent and infection is an important consideration; and the chronic phase in which vessel spasm, arterial damage, nerve damage and tissue atrophy are predominant. It is well to discuss treatment of these three phases separately, since the objectives are different.

The acute phase. As soon as possible, the frostbitten part should be thawed, not slowly, not on the radiator, not in front of a stove, but in the largest possible vessel of water, warmed to 100–112° F. (42–44° C.). A rectangular five gallon tin gasoline can with one side removed is an ideal container[5]. Great care has to be taken never to have the water warmer than 112° Fa. (44° C.) and expeditions, first-aid stations should always have a rugged thermometer, reading up to 150° Fa. Immersion in hot water should be kept up for about 20 minutes. It is painful and requires salicylates or demerol during the procedure. In patients with general hypothermia and slow respirations, narcotics are best avoided, so as not to depress the respiratory center.

In addition to local warming, general body warming is important. Hot liquids should be administered. Alcohol is not useful, except during the period of rewarming and only if the patient has

reached an environment where he will remain constantly warm thereafter.

If liquid rewarming is not feasible, the part can be placed against a warm abdomen, under the armpit or wrapped *loosely* in warm blankets after a sterile gauze dressing is applied.

Rubbing with snow, thawing in cold water, vasodilators, anticoagulants and the Korean intravenous cocktail of dextrose, heparin, procaine and alcohol, are not recommended. After rewarming, the part should not be bandaged tightly with elastic bandages, nor exercised. The patient should not be allowed to bear weight on recently rewarmed feet.

Because there is much vasospasm proximally to the frozen part, sympathetic block or sympathectomy may be performed early. Our experience with cervical sympathetic block in a superficial frostbite of the ear has been favorable. In another case, an early right lumbar sympathectomy in a case of symmetrical frostbite of both feet, resulted in early drying up and demarcation of the gangrenous toes of the right foot. Edema and wet gangrene persisted for six weeks on the unoperated side. This patient, operated on in 1951, has not had rapid thawing (Fig. 3).

The question of early sympathectomy for frostbite is not definitely settled. Wesolovski and his associates feel that early sympathectomy done on 27 patients within 10 days of the exposure has resulted in decrease of the local edema, earlier demarcation of non-viable tissue and faster healing.[10] Long term follow-up to see whether the late sequelae of frostbite can be avoided by early sympathectomy has recently become available.[11]

If the skin is broken, gentle cleansing with Dial soap, or a diluted (3%) hexachlorophene-G solution (Phiso-Hex) should be done. Blisters need not be punctured. A loose, dry, gauze dressing is applied and as soon as the patient's general condition is satisfactory, whirlpool baths are daily administered with the water at body temperature. A wide spectrum antibiotic, such as tetracycline or diemethylchlortetracycline (Declomycin) is administered in 150 mg. doses every six hours for a week.

Fig. 3.—Deep, fourth degree frostbite due to exposure in deep snow for six hours. Damage seemed identical on both sides, and mid-metatarsal amputations were necessary after demarcation. On the right sympathectomized side, demarcation, loss of edema and mummification developed in one week. It took the opposite, non-operated side six weeks to reach the same stage. From de Takats, G., Vascular Surgery, W. B. Saunders Company, Philadelphia and London, 1959.

Recently, with the availability of a hyperbaric oxygen chamber, the possibility of saving blue, pregangrenous toes with hemorrhagic blisters, by treatment in a high pressure oxygen chamber, has arisen, and one such case has been recently seen at our hospital.

Since at 3 atmospheres of 0_2, one finds 6 volume% of additional 0_2 in solution in addition to the 20 volume% carried by hemoglobin, the dissolved oxygen should be useful when the local blood supply has been seriously curtailed. While in completely devitalized tissue with an oxygen tension of zero, there is little reason to expect impressive benefits from hyperbaric oxygenation, where there is some collateral blood supply, the tissue oxygen tension could be raised and a

visible color change would be a good prognostic sign. Whether high pressure oxygen will diffuse through normal, inflamed or blistered skin is yet to be adequately studied.

In the *second stage*, the edematous, stiff digits or areas should be actively moved by the patient, and whirlpool baths are continued. Gangrenous toes or fingers are strictly left alone, allowed to demarcate and mummify. They are left open under a cradle without lights, or very loosely covered with dry gauze. No ointment, grease or local antibiotic is administered. Often a black, shriveled finger or toe, seemingly totally gangrenous, will shed a cast with pink, healthy skin under it. Amputation of digits should only be done after total demarcation has taken place and this may take several months.

The *third*, *late phase* is characterized by the results of vascular occlusion, vasomotor irritability, hyperhidrosis and partial nerve injury manifested by numbness, tingling and decrease of vibration sense. Dead tissue has all been shed or removed, but the remaining digits are atrophic, moist, sensitive to cold and heat. Our tests indicated that adaption to changes in temperature are dampened.[1] Wasting of the intrinsic muscles of the foot is noted and a hollowing of the sole and marked clawing of the toes occurs. Osteoporosis is frequent in spite of weight bearing. Patches of gangrene, when separated from viable tissue, may leave skin defects. Surprisingly enough, they can be covered by three-quarter thickness or full-thickness skin grafts. Such successful grafts have been placed on fingertips and on heels of frostbitten

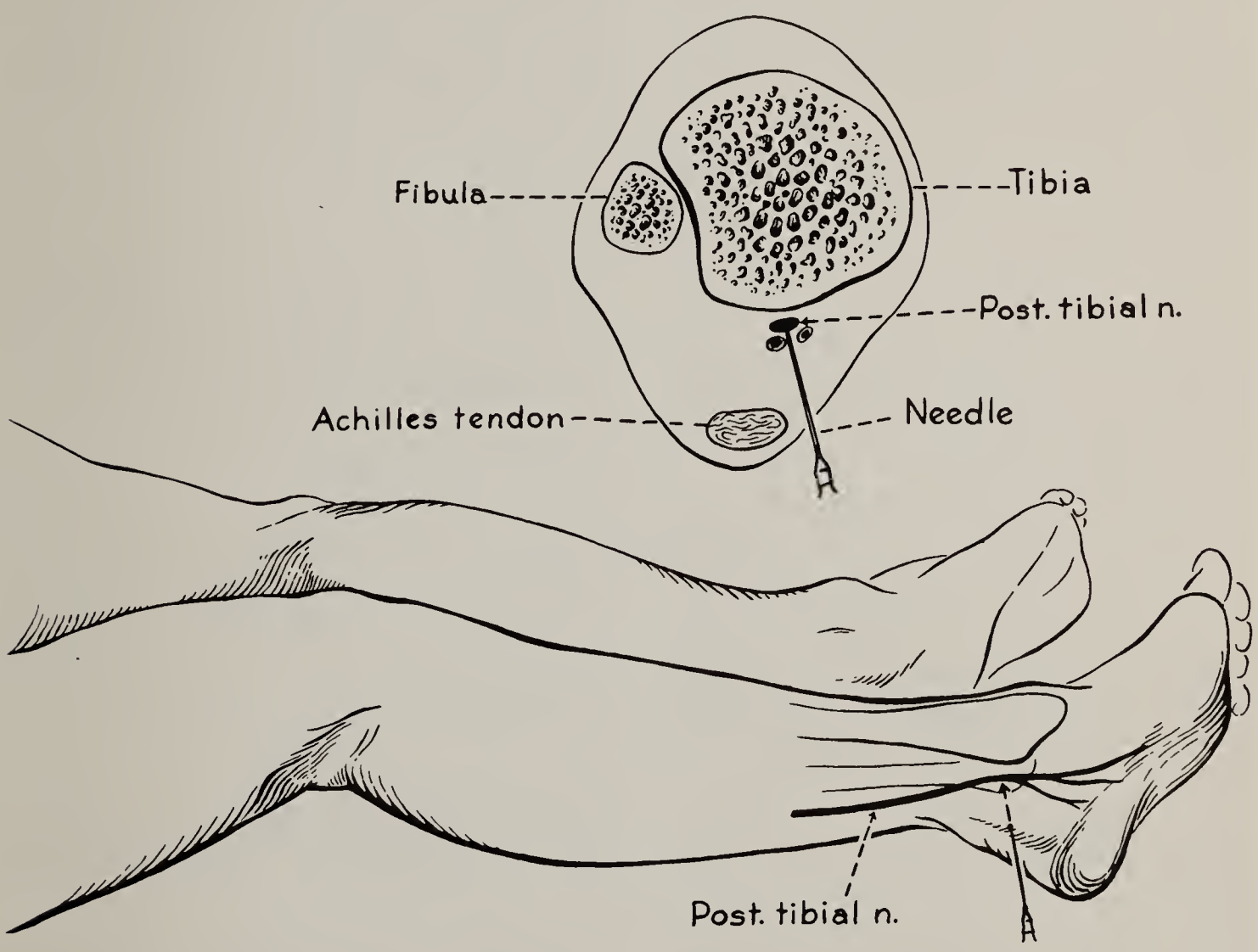

Fig. 4.—A 3-inch, 22 gauge needle is slowly inserted in a postero-anterior direction until paresthesia, radiating toward the heel and sole of the foot is obtained. Five cc. of 1% procaine solution is now slowly injected. Twenty minutes later, the heel, the sole of the foot and the plantar surface of the toes should be anesthetic. Testing for increase in skin temperature may now begin. From de Takats, G., Vascular Surgery, W. B. Saunders Company, Philadelphia and London, 1959.

young marines. This would be more doubtful on diabetic or arteriosclerotic individuals who suffered frostbite, but whose terminal circulation is affected by pre-existing vascular diseases.

It is important to differentiate here between the overwhelmingly vasospastic as against the neuropathic sequelae of cold injury.[6] In the former, sympathectomies have given excellent results in my hands; in the latter, one can easily aggravate the burning paresthesia by sympathectomy. A peripheral or paravertebral nerve block with procaine can differentiate the two conditions. In the mixed cases, if there is a good rise in skin temperature after a procaine block (Fig. 4), sympathectomy is useful. The burning and tingling, however, may not be affected. In veterans, a certain amount of compensation neurosis may exist. Such people have evidence of diffuse hyperhidrosis and increased vasomotor reactivity throughout the body and not only in the exposed part. They seem prone to cold injury.

DISCUSSION

One would think that the prevention and treatment of cold injuries must be as old as any medical endeavor, and truly there is nothing new under the sun. Nevertheless, there are recurrent fads and fancies. In this brief report, emphasis has been placed on; 1) rapid rewarming; 2) early sympathetic blocks; 3) dry dressings with avoidance of tight bandaging and ointments; 4) spontaneous demarcation of necrotic tissue, and; 5) late sympathectomies in case of sympathetic hyperactivity.

Naturally, prevention is more important, and hunters, skiers, explorers, mountain climbers and outdoor workers need careful indoctrination. As long as there are wars, and unless the characteristics of war change to atomic or germ warfare, men will be injured, immobilized and exposed in cold climates. The experience of the Korean war would indicate that large masses of the fighting force still suffer cold injuries.

SUMMARY

Prevention and treatment of early, intermediate and late stages of cold injuries have been presented. The fate of the affected part is mostly determined by the intensity and duration of the exposure to cold. However, early, intensive treatment may favorably influence the outcome and eliminate the end results of this injury.

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MATHEMATICAL MODEL FOR THE INDEPENDENT MODIFICATION OF RED BLOOD CELL MASS AND TOTAL BLOOD VOLUME

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During the past two decades exchange transfusions have been extensively used in the treatment of hemolytic disease of the newborn.[1–5] In spite of the success of this therapy in erythroblastosis fetalis and limited experience with exchange transfusions in older patients[6–10], little attention has been given to the application of these techniques in the management of polycythemia rubra vera or erythrocythemia where one of the objects of therapy is to reduce the red cell mass while controlling the total blood volume.

The purpose of this paper is to present two mathematical models that permit the independent modification of plasma and red cell constituents of the blood. Information derived from these models has been used to effect a prompt and predictable modification of total red blood cell volume and total blood volume. The models will be presented and an illustrative case reported.

MATHEMATICAL MODEL

The assumptions made in this model are that the cardiovascular system is represented by a closed elastic system of connecting tubes which contain circulating fluid of homogeneous composition. These assumptions are valid if the modification is accomplished over a relatively short period and if ample time is permitted for mixing of blood after each interchange.

The constituents of the model consist of plasma whose volume is denoted by P and red blood cells whose volume (total red blood cell mass) is denoted by R. The total blood volume is denoted by V where $V = P + R$. Modifications in the constituents are accomplished using a syringe through which additions or subtractions of the component volumes may be made. Alteration of the constituents of blood is permitted by the removal of a volume "v" of the contents of the system "V" followed by the injection of a volume "u" of plasma or blood whose hematocrit is different from that of the system "V". A cycle consisting of the removal of volume "v" followed by the injection of volume "u" is defined as an interchange.

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The following terms are defined for the development of the mathematical model:

R_0 = Initial red cell mass (measured in ml.) in the system
R_i = Red cell mass in the system following the ith interchange
R_n = Desired red cell mass after the last (nth) interchange
V_0 = Initial total blood volume (measured in ml.)
V_i = Total blood volume following the ith interchange
V_n = Desired total volume after the last (nth) interchange
v = Volume of blood removed from the system in each cycle
u = Volume of plasma or blood injected in each cycle
H_k = Hematocrit* of blood (or plasma) injected in each cycle
H_0 = Initial hematocrit* of system
H_i = Hematocrit* of the system after the ith interchange
H_n = Desired hematocrit* after the last (nth) interchange

*Body Hematocrit $= \dfrac{\text{Red Cell Mass}}{\text{Total Blood Volume}}$

Model A. Iso-volemic model for alteration of red cell mass or plasma volume. ($u = v$)

$$H_1 = H_0 - H_0\frac{v}{V} + H_k\frac{v}{V} = H_0\left(1 - \frac{v}{V}\right) + H_k\frac{v}{V}$$

$$H_2 = H_1\left(1 - \frac{v}{V}\right) + H_k\frac{v}{V} = H_0\left(1 - \frac{v}{V}\right)^2 + H_k\frac{v}{V}\left[\left(1 - \frac{v}{V}\right) + 1\right]$$

$$H_3 = H_2\left(1 - \frac{v}{V}\right) + H_k\frac{v}{V} = H_0\left(1 - \frac{v}{V}\right)^3 + H_k\frac{v}{V}\left[\left(1 - \frac{v}{V}\right)^2 + \left(1 - \frac{v}{V}\right) + 1\right]$$

Then, by induction

$$H_n = H_0\left(1 - \frac{v}{V}\right)^n + H_k\frac{v}{V}\left[\left(1 - \frac{v}{V}\right)^{n-1} + \left(1 - \frac{v}{V}\right)^{n-2} + \cdots + 1\right]$$

$$= H_0\left(1 - \frac{v}{V}\right)^n + H_k\frac{v}{V}\frac{\left[1 - \left(1 - \frac{v}{V}\right)^n\right]}{\left[1 - \left(1 - \frac{v}{V}\right)\right]}$$

$$= H_0\left(1 - \frac{v}{V}\right)^n + H_k\left[1 - \left(1 - \frac{v}{V}\right)^n\right]$$

$$= (H_0 - H_k)\left(1 - \frac{v}{V}\right)^n + H_k$$

Then

$$\frac{H_n - H_k}{H_0 - H_k} = \left(1 - \frac{v}{V}\right)^n \tag{1}$$

and

$$n = \frac{\log\left(\frac{H_n - H_k}{H_0 - H_k}\right)}{\log\left(1 - \frac{v}{V}\right)} \tag{2}$$

These equations permit the adjustment of the hematocrit in either direction. Thus, where a decrease in hematocrit is desired, plasma may be used to replace blood ($H_k = 0$), and

$$n = \frac{\log\left(\frac{H_n}{H_0}\right)}{\log\left(1 - \frac{v}{V}\right)} \tag{2a}$$

As the interchange volume v increases, n decreases. Thus in the limiting case (phlebotomy) $n = 1$ and $H_k = 0$. Then, the volume of blood to be removed to reduce the red cell mass to R_n is

$$v = V\left(1 - \frac{R_n}{R_0}\right) \tag{3}$$

If this procedure is used to correct a hemoglobin deficiency with suspended packed cells, equation (2) would be applicable.

By rearrangement of equation (2), total blood volume may be estimated by this procedure by determining hematocrits at the beginning and end of n interchanges.

$$\begin{aligned} V &= \frac{v}{1 - \left(\frac{H_n - H_k}{H_0 - H_k}\right)^{1/n}} \\ &= \frac{v}{1 - \text{antilog}\left(\frac{\log\left(\frac{H_n - H_k}{H_0 - H_k}\right)}{n}\right)} \end{aligned} \tag{4}$$

Model B. Model for the independent reduction of red cell mass and alteration of total blood volume. $(u \neq v)$

$$V_n = V_0 - n(v - u) \tag{5}$$

The red cell mass following the first exchange cycle is

$$R_1 = R_0 - \frac{R_0}{V_0} v = R_0\left(1 - \frac{v}{V_0}\right)$$

Similarly:

$$\begin{aligned} R_2 &= R_1\left(1 - \frac{v}{V_1}\right) = R_0\left(1 - \frac{v}{V_0}\right)\left(1 - \frac{v}{V_0 - (v - u)}\right) \\ &= R_0\left(\frac{V_0 - v}{V_0}\right)\left(\frac{V_0 - v - (v - u)}{V_0 - (v - u)}\right) \\ R_3 &= R_2\left(1 - \frac{v}{V_2}\right) = R_0\left(\frac{V_0 - v}{V_0}\right)\left(\frac{V_0 - v - (v - u)}{V_0 - (v - u)}\right)\left(\frac{V_0 - v - 2(v - u)}{V_0 - 2(v - u)}\right) \end{aligned}$$

By induction

$$R_n = R_0\left(\frac{V_0 - v}{V_0}\right)\left(\frac{V_0 - v - (v-u)}{V_0 - (v-u)}\right)\cdots\left(\frac{V_0 - v - (n-1)(v-u)}{V_0 - (n-1)(v-u)}\right)$$

$$= R_0\frac{\left(\frac{V_0 - v}{v-u}\right)\left(\frac{V_0 - v}{v-u} - 1\right)\left(\frac{V_0 - v}{v-u} - 2\right)\cdots\left(\frac{V_0 - v}{v-u} - (n-1)\right)}{\left(\frac{V_0}{v-u}\right)\left(\frac{V_0}{v-u} - 1\right)\left(\frac{V_0}{v-u} - 2\right)\cdots\left(\frac{V_0}{v-u} - (n-1)\right)}$$

Then

$$\frac{R_n}{R_0} = \frac{\left(\frac{V_0 - v}{v-u}\right)! \quad \left(\frac{V_0}{v-u} - n\right)!}{\left(\frac{V_0 - v}{v-u} - n\right)! \quad \left(\frac{V_0}{v-u}\right)!} \tag{6}$$

and from equation (5)

$$\frac{R_n}{R_0} = \frac{\left(\frac{V_0 - v}{v-u}\right)! \quad \left(\frac{V_n}{v-u}\right)!}{\left(\frac{V_n - v}{v-u}\right)! \quad \left(\frac{V_0}{v-u}\right)!} \tag{7}$$

Thus, if R_n, R_0, V_n, V_0, and v are known, solving for u must be done by a process of iteration, varying u such that both sides of equation (7) are approximately equal. Such manual computations are facilitated by the use of tables of logarithms of factorials.

The number of cycles n is determined by transposing equation (5)

$$n = \frac{V_0 - V_n}{v - u} \tag{8}$$

Where a computer facility is available, the value of u can be determined by iteration without logarithmic transformation, reducing the number of factors of the right side of Equation (7) to

$$\frac{R_n}{R_0} = \frac{\left(\frac{V_n}{v-u}\right)\left(\frac{V_n}{v-u} - 1\right)\left(\frac{V_n}{v-u} - 2\right)\cdots\left(\frac{V_n}{v-u} - \frac{v}{v-u} + 1\right)}{\left(\frac{V_0}{v-u}\right)\left(\frac{V_0}{v-u} - 1\right)\left(\frac{V_0}{v-u} - 2\right)\cdots\left(\frac{V_0}{v-u} - \frac{v}{v-u} + 1\right)} \tag{9}$$

A simpler equation is obtained using the calculus which is valid for cases where changes in red cell mass and blood volume per interchange are small with respect to the total red cell mass and blood volume.

$$R_i = R_{i1}\left(1 - \frac{v}{V_{i-1}}\right)$$

Then,

$$R_{i-1} - R_i = dR = \frac{vR}{V}$$

and

$$V_i = V_{i-1} - (v - u)$$

Then,

$$V_{i-1} - V_i = dV = v - u$$

$$\frac{dR}{dV} = \frac{v}{v-u} \cdot \frac{R}{V}, \qquad \text{and} \qquad \int \frac{dR}{R} = \frac{v}{v-u} \int \frac{dV}{V}$$

$lnR = \frac{v}{v-u} lnV + lnC$, where C is an arbitrary constant.

Then,

$$R = CV^{\frac{v}{v-u}}$$

Since

$$R_0 = CV_0^{\frac{v}{v-u}}, \qquad \text{then} \qquad C = R_0 V_0^{-\left(\frac{v}{v-u}\right)}$$

and

$$R_n = R_0 \left(\frac{V_n}{V_0}\right)^{\frac{v}{v-u}}$$

Since R_n, R_0, V_n, V_0, and v are known or determined before the transfusion procedure, then u is determined as a linear function of v.

$$u = v \frac{\log\left(\frac{R_0}{R_n} \cdot \frac{V_n}{V_0}\right)}{\log\left(\frac{R_0}{R_n}\right)} \tag{10}$$

A comparison of the calculated values of "u" for different values of "v" obtained by equation (9) performed by a computer and equation (10) using the calculus shows the two mathematical approaches to produce almost identical values within the technical limitations of the total procedure. Data from patient M. T. have been used to generate the calculated values of "u" using both mathematical techniques and the results are shown in Table 1.

ILLUSTRATIVE CASE REPORT

Mrs. M. T. (PSLH #760591) was an 83 year old patient who was admitted to the Presbyterian-St. Luke's Hospital for treatment of recurrent thrombophlebitis. During the three months prior to admission, the patient had experienced vague upper gastrointestinal symptoms, had one episode of dizziness and had noted some loss of memory. During the two months prior to admission, the patient had been treated for two episodes of thrombophlebitis, and at the time of this admission had evidence of thrombophlebitis in her left calf. In addition to the findings compatible with thrombophlebitis in her left calf the patient had a palpable spleen.

The laboratory studies revealed a hemoglobin of 19.8 gm%, a hematocrit 63% and a white blood cell count 11,750 mm^3. The differential white blood cell count was as follows: Neutrophils 48%,

bands 37%, lymphocytes 7%, monocytes 6% and eosinophils 2%. The platelet count was 372,500 mm^3. The red blood cell mass, determined with chromium ^{51} labeled RBC's was 58.6 ml/kg, the plasma volume was 48.9 ml/kg and the total blood volume was 107.5 ml/kg. The bone marrow was hyperactive with little fat. Megakaryocytes were increased and there was hyperplasia of the myeloid and erythroid series. An intravenous pyelogram was normal and oxygen saturation studies were within normal limits. The patient's hematologic disorder was classified as polycythemia rubra vera. The decision was made to effect an immediate reduction in the patient's red blood cell mass in hopes of preventing recurrent episodes of thrombosis.

The patient weighed 42.3 kilograms, had a red blood cell mass of 2478 ml and a total blood volume of 4547 ml. It was elected to reduce her red blood cell mass to 1165 ml and total blood volume to 3840 ml.

The volumes of blood to be removed and the volumes of plasma to be replaced with each interchange were selected according to the following considerations: 1) The entire transfusion procedure should not exceed three hours. Estimating that each complete interchange could be accomplished in approximately five minutes, the maximum number of such interchanges was then determined to be 36. 2) Due to the patient's condition, it was felt advisable to remove no more than 100 ml of blood with each interchange.

The computer printout for equation 9 for this particular patient is shown in Table 2. Reference to this table indicates that removal of volumes of 100 ml per interchange would effect the desired modification after thirty-one such interchanges if the replacement volume of plasma were 77 ml per interchange. This schedule of interchanges was carried out by removing whole blood through an arterial needle and reinfusing aged plasma into an indwelling catheter in the superior vena cava.

TABLE 1

Calculated Values of "u" for Various Values of "v"

Volume of Blood Removed Per Exchange (v)	Calculated Volume of Plasma Replaced Per Exchange (u)	
	By Equation (9) (Computer)	Equation (10)
50 ml.	38 ml.	39 ml.
75	58	58
100	77	77
125	96	97
150	115	116
175	135	136
200	154	155

The patient tolerated the procedure well. Intermittent monitoring of the patient's central venous pressure and brachial arterial pressure showed no significant change during the procedure. At the completion of the partial exchange transfusion, a repeat red blood cell mass was determined using chromium^{51} tagged red blood cells. The initial, desired and achieved blood volumes are shown in Table 3.

DISCUSSION

Since the introduction of the technique of exchange transfusions in 1921[10], several papers have been published discussing the mathematical approach to the determination of the percent of donor blood remaining in the body after repeated replacement transfusions.[9,11–17] In general these formulas have considered the case where the total infused volume equals the total removed volume with little regard for the final red blood cell mass. The models presented in this paper permit the independent alteration of final total blood volume and final red blood cell mass. This method permits prompt correction of blood volume abnormalities in an efficient manner and permits the physician to preselect the time during which this correction is accomplished, the magnitude of the change desired and the size of each interchange.

The most efficient approach measured in time is to remove and replace the maximum volume of blood constituents the fewest number of times. Conversely the continuous infusions and outflows are most inefficient. Furthermore continuous flow models do not fulfill the assumptions

SECTION OF BIOSTATISTICS AND EXPERIMENTAL DESIGN
PRESBYTERIAN-ST.LUKES HOSPITAL

SCHEDULES FOR MODIFYING RED CELL MASS AND BLOOD VOLUME

PATIENT M.T. HOSP.NO. 760591 ROOM NO. 1117

PHYSICIAN O BRIEN DATE 1/ 5/65

BLOOD REMOVED PER EXCHANGE	PLASMA REPLACED PER EXCHANGE	NUMBER OF EXCHANGES	RED CELL MASS	BLOOD VOLUME	BODY HEMATOCRIT
0	0	0	2478.	4547.	54.49
50.	38.	58.91	1223.	3840.	31.87
75.	58.	41.58	1173.	3840.	30.56
100.	77.	30.73	1184.	3840.	30.83
125.	96.	24.37	1189.	3840.	30.97
150.	116.	20.79	1167.	3840.	30.40
175.	135.	17.67	1172.	3840.	30.53
200.	154.	15.36	1175.	3840.	30.62

DESIRED LEVELS- RED CELL MASS 1165.

- BLOOD VOLUME 3840.

TABLE 2

of our present models and thus result in considerable lack of precision.

The models described have been used for the rapid alteration of red cell mass associated with erythrocythemia. These formulas, with modification, would be applicable to the case requiring transfusion where either the blood volume and hematocrit are decreased or where the total blood volume is increased and the red blood cell mass is decreased. Although such problems are frequently met in the clinical practice of medicine they are efficiently and routinely handled by the transfusion of either whole blood or packed red blood cells. Lastly, the isovolemic model has potential usefulness in the adjustment of other intravascular substances such as abnormal proteins, various coagulation factors and circulating toxic substances.

TABLE 3

Data on Blood Volumes
Patient M. T.

	Before Transfusion	After Transfusion	
		Desired	Achieved
Red Cell Mass	2478 ml.	1165 ml.	1138 ml.
Total Blood Volume	4547 ml.	3840 ml.	3806 ml.

SUMMARY

A mathematical model has been presented which permits the prompt and predictable modification of plasma volume and red blood cell components of blood. The method permits alterations of these constituents in an efficient manner within the restrictions imposed by the general health of the patient. The judgment as to the volume of blood removed and the volume of fluid infused in the patient with each interchange remains with the physician.

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MUCOANTIBODY IN THE HUMAN VAGINA

Elizabeth K. Straus, M.D.

INTRODUCTION

During the distinguished history of immunology the major proportion of work has been done with humoral or circulating antibody. Relatively little attention has been paid to antibody produced locally and combined with mucoprotein on various mucosal surfaces. However, the defense mechanism in many serious infections depends for effective immunity on the local production of mucoantibody. Local excitation of antibody was first performed by Bursuk in 1928 when he demonstrated agglutinins to typhoid bacilli and staphylococci in the cornea of one rabbit eye. No antibody could be demonstrated in the circulation or in the other cornea. In 1959, A. E. Pierce[1] made an exhaustive study of the literature relative to antibodies at mucus surfaces. Mucoantibody has been found in the alimentary tract, udder, reproductive and urinary tracts and the respiratory tract. Mucoantibody to *H. pertussis* and the influenza virus in the latter appeared simultaneously with circulating antibody and the titers varied with the serum titer. It was concluded that this mucoantibody was derived by filtration from the serum. On the contrary, effective immunity to *B. Abortus* and *Tr. foetus* in the bovine vagina, as well as to cholera, poliomyelitis, bacillary dysentery and certain Salmonella infections in the intestines of animals and man was largely dependent on the mucoantibody titer, which appeared earlier and was unrelated in titer to the circulating antibody.

A careful and comprehensive experimental approach to the study of intestinal or copro-antibody in intestinal mucus has been carried out by Burrows[2, 3], and there is considerable evidence that mucoantibody can be found locally in the bovine vagina and the intestines of all species. Copro-agglutinins to the coliforms and enteric pathogens have been found in man and experimental animals and are thought to be the basis for the normal microbial flora of the intestinal mucosa.

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In addition to the immune response to *Tr. foetus* and *B. abortus* demonstrable in the bovine vaginal mucus, antibody to homologous sperm has been found in the rabbit uterus and vagina following the local application of sperm or testis by Pommerenke[4] in 1928. In 1940 Parsons and Hyde[5] reported antibody in the serum and uterus of both rat and rabbit after the introduction of homologous and heterologous sperm into the vagina. Lindahl[6] in 1956 found anti-sperm agglutinins in the cervical secretions of human females shortly after ovulation and in the second trimester of pregnancy. Hemagglutinins to Group A and Group

B red cells have been found in the cervical secretions of Group O women by Behrman[7] in 1958. He suggested that infertility might at times be caused by such antibodies. Other than these, no reports of vaginal mucoantibody were made prior to 1961.

The antigenic capacity of various fractions of animal serum and testicular homogenate, as well as of washed seminal or epididymal sperm, has been long established and the subject has been well reviewed by Katsh[8]. As long ago as 1938 Henle[9] detected distinct head and tail antigens in human sperm. Weil[10] has reported that species and organ specific antigens, absent in epididymal sperm, are firmly attached to spermatozoa after contact with seminal fluid. As many as 16 distinct antigens have been detected by Rao[11] in the whole serum of the water buffalo by gel diffusion techniques. Of these, three appear to be restricted to the spermatozoön itself. Edwards[12] has found species specific and blood group isoantigens of the ABO, MN and Tja systems in the cell membrane of human sperm. Tyler[13] has shown that antifertilizin, which is a component of semen in all species, can excite antibodies which interfere with fertilization in lower animals.

Sterility in the male is readily produced by parenteral injection of homologous sperm or testicular homogenate, both of which elicit autoantibody de-

TABLE I. AGGLUTININ RESPONSE TO PARENTAL TYPHOID VACCINE

		A (1940)*		B (1957)*		C (none)*		D (none)*		E (none)*	
	Days After Inoc.	Mucus	Serum	Mucus	Serum	Mucus	Serum	Mucus	Serum	Mucus	Serum
Immune Response — Primary	0	0	0	0	0	0	0	0	0	0	0
	3	10		10		0		0		10	
	7			10	0	10	10			10	
	10			50		100				50	
	17	50	200	100	200	50	1000	100	2000		
	21	100						100			
	24	100	5000			100	500	100	2000	100	500
	28			100		50		100		100	
	31	10	500	10	200	20	500				
	33									100	500
	35	10		10		50				50	
	51	0		0		0		50	1000	50	
Immune Response — Secondary	0	0	200	0	500	0	500	0	20	0	
	3	0		0		20		200			
	7	0	200			20	1000	200	1000	100	500
	10	20				20		100			
	14	50	200	20	100	100	500			100	
	17	50		100						200	
	21			100	200					200	
	24			100		100		10	1000	200	
	28					50					
	31	50		50		50		10		200	1000
	35	100	500			200		50	500		
	38	10		50		20		20			
	42			100	2000	50	1000			200	
	45	0									
	47									100	
	49	50		10	200			0			
	51									100	5000
	52	20	1000	0		10					
	54									20	
	56			0	100						
	63	0	1000			100	500				
	68									0	
	70					0					
	72									0	5000

*Date of prior typhoid immunization.

structive to the cells of the testis. Many efforts have been made to immunize female animals by parenteral injection of homologous sperm or testis with adjuvant. Although high antisperm serum titers have been obtained by this method, no clear cut impairment of fertility has been observed. Recently Behrman[14], Ashitaka[15] and Edwards[16] have found sperm agglutinius, precipitins and reduction in numbers of motile and/or immotile sperm in the uterine and vaginal fluids of immunized female animals. No correlation was found between circulating antibody and infertility, but Ashitaka and Edwards agreed on some correlation between reduced numbers of motile and/or immotile sperm in the genital tract and reduced fertility.

METHODS AND RESULTS

With this background an attempt was made in 1960 to determine whether mucoantibody could be deliberately induced in the human female vagina. Five volunteers were immunized by parenteral injection to commercial typhoid-paratyphoid vaccine and the agglutination titers of *S. Typhosa 901* in the serum and vaginal mucus were followed for 7-10 weeks. (Table I). The mucus was obtained by swabbing the cervix and vagina with a cotton tampon moistened with 5 ml. of normal saline. The mucus and saline were squeezed out, centrifuged to remove cells and debris and titrated by the classical method. The mucus was assumed to be in 1-5 dilution before titration. Agglutinating antibody, in accordance with Pierce's finding in the bovine vagina, appeared in the vaginal mucus of all five women before serum antibody was detected. The titer did not rise above 200 and disappeared in 5-7 weeks while serum antibody was still present.

Subsequently eight volunteers were immunized by the local application of typhoid soluble antigen to the cervix and vagina. The antigen was prepared by sonic lysis of a heat inactivated, saline suspension of an 18 hour culture of *S. Typhosa 901* diluted to a protein N content similar to that of commercial typhoid vaccine. A junior Tampax soaked with 10 ml. of this antigen was applied to the cervix and vagina for 72 hours and agglutinin titers were followed as above.

TABLE II. AGGLUTININ RESPONSE TO LOCALLY APPLIED SOLUBLE ANTIGEN

Days After Inoc.	Gl (1952)*		Hi (1955)*		St (none)*		We (1954)*		Co (none)*		Com (1953)*		Mo (1960)*		Bl (1960)*	
	M	S	M	S	M	S	M	S	M	S	M	S	M	S	M	S
0	0	0	0	0	0	0	0	0	0	0	0	0	0	500	0	5000
3									100		200				200	
4	0		0		200		2000	5000								
6									200	200	500	2000				
7					100	200	1000									
8	100		200	200												
11	100	500			1000		1000						500	2000		
13			100						500	100	100	2000			1000	
14					100	200	200	500								
15	2000												2000			
17									2000		2000					
18	500	100			2000		500						200	1000		
20									20	20	0	500				
21					0	0										
22	1000		2000	200									1000			
24							20	1000	20		0					
25	20		0										20	1000		
27					100	100			200	1000	50	500			0	500
28	20		0	1000			20						20			
32	200	200	50												50	
43	1000														20	

(Immune Response)

* Date of prior typhoid immunization M = mucus; S = serum.

TABLE III. HEMAGGLUTININ RESPONSE TO BOVINE SERUM ALBUMIN (B.S.A.)

Days after inoc.	Subject																	
	Hc			Co			We			Hi			Mo			Bl		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
0	0	200	0	0	0	0	0	200	0	0	200	0	0	500	0	0	0	0
3										0								
4				0		0	1000		0				0		0	0		0
6										500	200	0						
7				100	500	0	250	500	0							0	1000	0
10										50		0				250		0
11				1000		0	0		0				0	10	0			
13	50	200	0															
14										5000	0	0	0		0	100	1000	0
17																0		0
18	0	200	0	50	500		0	1000	0				250	500	0			
20	100		0															
21				50		0	0	500	0				250		0			
24	500	1000	0															
25				0	500		0						100	500	0			
26										100	1000	0				0	500	0
28	0		0															
29				0		0	0		0				0		0	250		0
31	0	2000	0															
32				0	50		0	0	0	0			0	2000	0	0	500	0
33										0	1000	0						

1 = Mucus
2 = Serum
3 = Inhibition Tests

(Table II) Titers of 100-200 were found in three days and peak titers of about 2000 were reached in 15 days. Serum agglutinim was in general lower than that obtained by parenteral injection. The mucoantibody titer declined in 3-4 weeks but tended to reappear in 6-7 weeks when the serum titer had risen.[18]

In the next experiment five volunteers were immunized in the same way to the weak antigen, bovine serum albumin or BSA. Ten ml. of 10% BSA was applied to the cervix and vagina for 72 hours as described above. The serum and vaginal mucus were tested for agglutinating antibody by Ingraham's[17] modification of the hemagglutination technique. Inhibition tests were also done using 1 gtt. of 10% BSA in each cup (Table III). It was evident that antibody to a weak antigen could also be produced by local vaginal application of antigen.

An attempt was then made to apply this model system to the problem of antisperm antibody in women. Sperm soluble antigen (SSA) was made by pooling 30-40 specimens of normal human sperm, washed 3x in normal saline and then suspended in about 15 cc. of saline. The semen was collected by Dr. Norris G. Heckel in the course of routine examination of the husband in sterility cases. The pool which had been stored in the deep freeze, was subjected to sonic lysis, clarified by centrifuging, and the protein-N value determined. Local vaginal immunization was carried out with approximately 100 mcg. of protein-N in nine post menopausal women. Hemaglutination and latex agglutination tests were carried out, coating the red cells and latex particles with SSA as prepared above. Sperm immobilization and sperm agglutination tests were also performed (Table IV). Difficulties were encountered because of the heterogeneous character of SSA containing, as it does, so many different antigens including the blood group antigens. Blood serum agglutination tests were always strongly positive, no doubt because of the presence of ABO antigen on the particle. It also appeared that spontaneous agglutination by vaginal mucus, which might contain traces of blood or other agglutinating factors, could cause confu-

sion. The results reported here contain only those positive agglutinations which could be reproduced and also inhibited by 1 gtt. of SSA.

Since, in spite of all precautions, the agglutination tests for antibody to SSA did not appear to be entirely satisfactory, the next experiment employed, as a test system, the number of motile and immotile sperm in the cervical mucus following coitus, as read in the standard Sims-Hühner test. Eight women volunteers of child bearing age were observed in the postcoital test before and after local immunization by SSA. Seven of these women were using Enovid (5 mg. daily) as a contraceptive. (Table V.) The eighth was using no contraceptive.

TABLE IV. RESPONSE TO HUMAN SPERM SOLUBLE ANTIGEN (S.S.A.)

Days after inoc.	Subject																							
	Bow				Br				Du				Gi				Ma				Ro				Rob				St				Sm			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
0																																				
3						+											+		++		+		++												
4																	++	++											++							
7	+	+	+	+		+					++		++								++															
9													++	++																	++					
10						++	++														++				+		++									
11	+	+	+	+					+		++																						++	++		
14	+		++										++	++											+		++		+							
15									++	++																								++	++	
17														++	+										+											
18									++	++																										
21																																				
24					++	++																														
25																																				
28							++																						+							
31					++	++											+		++																
37																	+		++																
38			++						+		++		+		++		+				++															
43	+		++														+				++				+								+			
																									+											

1 = Hemagglutination
2 = Latex agglutination
3 = Sperm agglutination
4 = Sperm immobilization

(Table VI.) One subject, Gir, in Table V failed to show motile sperm in preimmunization postcoital tests, and in the subject B1, in Table VI, motility was seen only during an ovulatory period of three days. In all other subjects the preimmunization motility of the sperm was quite consistent even though the ingestion of Enovid produced a postovulatory cervical mucus traditionally hostile to sperm. Although the results indicate that SSA prepared in this way is a rather weak antigen, there was definite, if irregular, reduction in sperm motility which returned after immunization was discontinued in most of these subjects. This reduction is best accounted for by assuming the presence of anti-sperm antibody excited by SSA. After the first immunization of the subject Bl in Table VI, sperm motility was virtually eliminated, but a second attempt at immunization about 8 months later failed to reduce motility until the sixth local application of antigen. It is interesting to note in this young woman of proved fertility and with fully patent Fallopian tubes, that, after immunization, four exposures to extremely motile sperm on or near the day of ovulation did not lead to pregnancy. It is also interesting to note that, in accordance with Lindahl's finding of anti-agglutinin in the cervical mucus, no evidence of sperm agglutination was ever seen, even though in one instance the sperm exceeded 100/h.p.f.[19]

TABLE V.

POST COITAL RESPONSE OF SUBJECTS ON ENOVID TO HUMAN SPERM SOLUBLE ANTIGEN (S.S.A.)

Gir—para 3

1	2	3	4
—	9	0	+ + + +
—	3	0	+ + + + +
—	9	0	+ + + + +
—	9	0	+ + + + +
—	4	±	+ + + + + +
—	10	0	+ + + + +
—	10	0	+ + + + +
—	10	0	+ + + + +

Immunized—72 hrs.
5ml. SSA N = 12μg./ml.

7	4	+	+ + + + +
14	11	0	+ + +
23	12	±	+ + + +

Immunized—72 hrs.
5ml. SSA N = 43μg./ml.

7	11	0	+ + + +
11	9	0	±
13	4	±	+ + + + + +
17	14	0	+ + + + +
20	12	±	±

Immunized—72 hrs.
5ml. SSA N = 80μ/ml.

4	12	0	+ + + + +
6	5	±	+ + + ±
11	12	0	+ + + + +
13	12	0	±
18	11	0	+
25	11	0	+ + + + +

Immunized—72 hrs.
5ml. SSA N = 20μg./ml.

6	12	0	±
8	12	0	+
10	12	0	+ + + +
13	12	0	+ + + + +
17	12	0	±
21	4	0	+ + + + +

Mei—para 3

1	2	3	4
—	7.5	+ +	+ + + + +
—	3.5	+ + + +	+ + + + +
—	7.5	+ + + +	+ + + + +
—	9.5	+ +	+ + + + +
—	10	+ +	+ + + +
—	10	+ +	+ + + +
—	10	+ + +	+ + + + +

Immunized—72 hrs.
5ml. SSA N = 12μg/ml.

4	10	0	+ + + + +
8	10	0	+ + + + +
11	10	±	+ + + + +
18	7	±	+

Immunized—72 hrs.
5ml. SSA N = 43μg/ml.

4	10	+	+ + + + +
8	10	+ + + + +	+ + + + +
11	3	±	+ + + + +
18	3	+	+ + +
22	10	±	+ + +

Immunized—72 hrs.
5ml. SSA N = 80μg/ml.

4	10	±	+ + +
8	3	+ + + +	+ + + +
11	10	±	+ + +
15	10	±	+ + + + +
18	10	+ + + +	+ + + +

Wo—nullipara

1	2	3	4
—	12	+ + + +	+ + + +
—	10	+ +	+ + + +
—	10	+ + + + +	+ + + + +
—	10	+ +	+ + + +
—	10	+ + + +	+ + + +
—	10	+ + + +	+ + + + +
—	10	+ + + +	+ + + + +
—	10	+ +	+ + + +
—	10	+ + + +	+ + + + +
—	10	+ + + +	+ + + +

Immunized—80 hrs.
5ml. SSA N = 12μg/ml.

4	10	±	+ + + + +
7	10	+ + + +	+ + + +
11	10	+	+ + + + +
14	10	+	+ + + + +

Immunized—72 hrs.
5ml. SSA N = 12μg/ml.

4	10	0	+ + + + +
7	10	±	+ + + + +
11	10	±	+
14	10	±	+ + + + +
18	10	±	+ + +
20	10	+ + + + +	+ + + + +

* = previous immunization
1 = days after immunization
2 = hours after coitus
3 = motile sperm in cervical and/or vaginal mucus
4 = immotile sperm in cervical and/or vaginal mucus

± = 1-10 sperm/whole preparation
\+ = 10-50 sperm/whole preparation
++ = 50-100 sperm/whole preparation
+++ = 100-400 sperm/whole preparation
++++ = 1-4 sperm/low power field
+++++ = 1-10 sperm/high power field
++++++ = 10-50 sperm/high power field

TABLE V. (Continued)

*Pag—para 4

1	2	3	4
—	10	+ + +	+ + + +
—	10	+ + +	+ + + + +
—	10	+ + +	+ +

Immunized—72 hrs.
5ml. SSA N = 80μg/ml.

4	10	+ + +	+ + + + +
11	10	+ + + +	+ + + +
15	10	±	+
21	8	±	+ + + +

Immunized—72 hrs.
5ml. SSA N = 40μg/ml.

7	10	0	+ + + + +
14	10	0	±
20	9	0	0
25	10	±	+ + + +
46	10	±	±
59	10	±	+ +

Wil—para 3

1	2	3	4
—	10	±	+ + + + +
—	3	+ + + + + +	+ + + + + +
—	2	+ +	+ + + + +
—	9	+ + + + + +	+ + + + +
—	9	+	+ + + + +
—	9	+	+ + + +

Immunized—72 hrs.
5ml. SSA N = 80μg/ml.

4	2	+ + + + + +	+ + + + + +
8	7	0	+ + + + +
13	9	+ + + + +	+ + + + + +
15	8	±	+ + + + +

Immunized—72 hrs.
5ml. SSA N = 80μg/ml.

28	9	±	+ + + + +

Immunized—72 hrs.
5ml. SSA N = 16μg/ml.

6	8	0	+ + + + +
10	7	0	+ + + + +
14	4	0	+ + + + +
29	9	±	+ + + + + +
49	4	+ + + + +	+ + + + + +

LaP—para 4

1	2	3	4
—	10	+ + + +	+ + + + +
—	10	+ + + +	+ + + + +
—	10	+ + + +	+ + + + +
—	10	+ +	+ + + +

Immunized—30 hrs.
5ml. SSA N = 4μg/ml.

3	10	±	+ +
7	10	±	+ +
15	10	±	+ +
18	10	+	+ +

Immunized—72 hrs.
5ml. SSA N = 8μg/ml.

7	10	+	+ +
11	10	±	+
22	10	0	±
25	10	±	±
32	10	+	±
38	10	+	+
47	10	0	+

*Na—nullipara

1	2	3	4
—	8	+ + + +	+ + + + +
—	8	+ + + + +	+ + + + +
—	8	+ +	+ + + + +
—	8	+ + + + +	+ + + + +

Immunized—72 hrs.
5ml. SSA N = 80μg/ml.

3	8	+ + + + +	+ + + + +
7	8	+ + + +	+ + + + +
11	8	±	+ + + + +
14	8	+ + +	+ + + + +
17	8	0	+ + + + +
21	8	+ + + + +	+ + + + + +
28	8	0	+ + + + +

Immunized—72 hrs.
5ml. SSA N = 40μg/ml.

4	8	0	+ + + + +
7	8	+	+ + + + +
10	8	+ + +	+ + + + +
15	8	0	+ + + + +
17	8	0	+ + + + +
25	8	+ + + +	+ + + + +

DISCUSSION AND CONCLUSIONS

These experiments suggest that antibody to various antigens can be produced in the vaginal and cervical mucus and that this can be done more effectively by local than by parenteral inoculation. There is some indication that washing and sonic lysis of such an immunizing agent as human sperm may unmask an effective antigen, for intact spermatozoa protected by seminal fluid are certainly not antigenic. Other workers who have used epididymal sperm as an antigen have always been forced to use Freund's adjuvant in addition. In these experiments where no adjuvant was used, evidence of mucoantibody has been obtained.

There is no doubt that the complexity of SSA makes it difficult to assess results in classical antigen-antibody reactions using this antigen. The presence of ABO antigens, and the ubiquity of antibody to these antigens, especially in secretions, make for a particularly confusing situation.

However, there is evidence in these studies that an effective anti-sperm, and

TABLE VI. POST COITAL RESPONSE OF SUBJECT WITHOUT CONTRACEPTIVE TO HUMAN SPERM SOLUBLE ANTIGEN (S.S.A.)

Subject B1— para 2

Days after Immunization	Hours after coitus	Days before ovulation	Sperm in cervical mucus	
			Motile	Immotile
—	9	3	+ + + + + +	+ + +
—	9	3	+ + + + + +	+ + +
Immunized 5ml. SSA N = 11.31mcg/ml. 72 hrs.				
7	9	0	±	+ + + + + +
83	9	1	+ + + + +	+ + + + + +
184	9	1	+ + + + + +	+ + + +
210	9	1	+ + + + + +	+ + + +
Immunized 5ml. SSA N = 40mcg/ml. 72 hrs.				
Immunized 5ml. SSA N = 20mcg/ml. 72 hrs.				
Immunized 5ml. SSA N = 60mcg/ml. 72 hrs.				
7	8	0	+ + + + +	+ + + + + +
Immunized 5ml. SSA N = 70mcg/ml. 72 hrs.				
8	10	3	+ + + + + +	+ + + + + +
11	10	0	+ + + + + +	+ + + +
Immunized 5ml. SSA N = 70mcg/ml. 72 hrs.				
9	10	0	+ + + + + +	+ + + +
Immunized 5ml. SSA N = 70mcg/ml. 72 hrs.				
8	10	0	+ + + + + feebly	+ + + + +
Immunized 5ml. SSA N = 170mcg/ml. 72 hrs.				
9	10	1	0	+ + + +
10	6	0	0	+ + + + +
Immunized 5ml. SSA N = 188mcg/ml. 72 hrs.				
8	8	2	0	+ + + + +
9	8	1	0	+ + + + +
10	8	0	0	+ + + + + +
32	9	0	+ + feebly	+ + + + + +
51	9	0	+ + feebly	+ + + + +
79	7	2	+ feebly	> 100/hpf
81	8	0	+ feebly	+ + + + +
102	8	2	+ + + +	+ + + + +
104	6	0	+ + + +	+ + + + +

therefore contraceptive, antibody may be excited in the cervical mucus by the simple application of some antigenic fraction of sperm to the cervix and vagina. Purification of the most effective antigenic fraction by some method such as electrophoresis, and the discovery of a fraction, such as purified antifertilizin, which could be obtained from other mammalian species, would greatly facilitate further studies on the feasibility of immunological types of contraception.

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CURRENT CONCEPTS IN LIPID METABOLISM

WILL G. RYAN, M.D.

A low fat diet fills a man with gas and self-righteousness.
Attributed to Sir Jonathan Hutchinson

The last several years have seen a considerable expansion of the study of lipid metabolism, largely because of its presumed relation to the genesis of atherosclerosis. So much information has accumulated so rapidly that it is difficult to digest it into a meaningful picture. This review will attempt such a digestion and hopefully will do so without provoking too much dyspepsia. For the interested reader, references to recent and more extensive reviews will be found in the bibliography.[1,2,3,4]

TYPES

The principal lipid types found in the body are four: triglycerides (neutral fat), phospholipids, cholesterol and free fatty acids. Although these compounds are structurally and functionally somewhat diverse, they are grouped together largely because of their insolubility in water and solubility in non-polar solvents.

FUNCTIONS

The primary function of triglycerides is storage of energy—the storage capacity being limited, apparently, only by the willingness and ability of the individual to tolerate it. Since storage of carbohydrate as glycogen is quite limited (about 300 gm. capacity); it could not sustain life for more than a day. A longer fast would require drawing on protein stores which are also somewhat limited. Much of the dietary carbohydrate is converted to triglyceride before being utilized.

Triglyceride is not released from fat tissue as such, but is hydrolyzed to its two components, free fatty acids (FFA) and glycerol by adipose tissue lipases which are apparently under hormonal control. Free fatty acids then enter the blood and are transported to all organs where they are readily metabolized for energy. In the fasting state they are the primary energy source for all tissues, excepting the brain which depends primarily on glucose. The fate of the glycerol released has not been quantitatively assessed, but is certainly utilized for energy and probably plays a significant role in the reformation of glucose. In this way, fat tissue in its glycerol moiety can supply calories to the brain under conditions of a prolonged fast, thus sparing protein. Epinephrine appears to play a prime role in mobilization of fat as fatty acids and has been shown to activate a tissue lipase *in vitro*. Insulin apparently suppresses the mobilization of fatty acids. These two antagonistic effects probably exert the prime control on the availability of fat for energy. In the presence of adequate carbohydrate (after a meal) the fatty acid levels in plasma fall because the elevated glucose and insulin levels prevent their being released from fat tissue. Other hormones (ACTH, GH, TSH, thyroxin, cortisol) also have FFA mobilizing effects, but these probably play a secondary or supportive role, Cholesterol functions as a structural component of cells, as a precursor of bile acids and steroid hormones, and probably

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other substances as yet ill-defined. Phospholipids also function as structural components of cells, particularily in the nervous system, and may serve in intracellular transport of the fatty acids to mitochondria.

Some idea of the importance of cholesterol and phospholipids, structurally, may be realized by the fact that these are the major components of an egg yolk which, along with the albumin, are formed into the completed chick.

LIPIDS IN BLOOD

Lipids are found in blood, presumably, because they are on their way from one part of the body to another. Because of their insolubility in water special vehicles are necessary for their transport. Thus *all* lipids found in blood are in combination with proteins to facilitate their transport—the combination is called, naturally enough, a lipoprotein and, triglycerides, phospholipids and cholesterol travel together in various combinations in these particles of varying sizes and densities. The protein moiety of the lipoproteins are special types of globulins which have an avidity for lipids. FFA travel separately, bound to albumin. These same lipoproteins when electrophoresed travel in the α and β globulin areas and are thus called the α and β lipoproteins. The density is largely determined by the triglyceride content of the particles—the more triglyceride present the less dense. Thus, the very low density lipoproteins are almost entirely triglycerides with very little protein, whereas the high density lipoproteins are composed of cholesterol, phospholipid and protein. (See Table 1.)

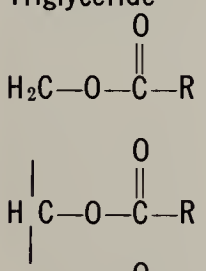
TABLE 1—Plasma Lipids

Lipoprotein Class	Sf	Density	Electrophoresis	Diameter	Percentage Composition			
					Protein	TG	Chol	PL
Chylomicrons	10,000 ± 5,000	~0.94	α2	5,000 Å	2	81	8E, 2F 10	7
VLDLP	20 — 400	0.96 — 0.99	α2	300 — 700 Å	10	55	5E, 8F 13	22
LDLP	0 — 20	1.032	β	190 Å	21	11	37E, 8F 45	23
HDLP		>1.036	α	50 — 300 Å	50	6	15E, 3F 18	26
FFA—Bound to Albumin								

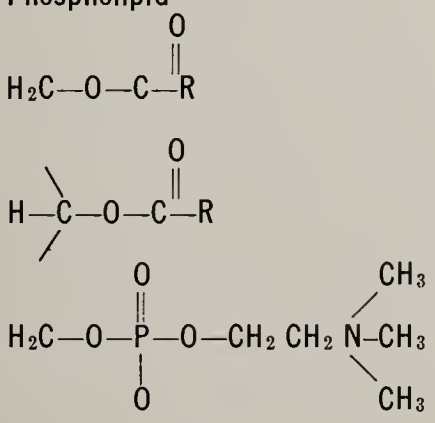
Numbers in percentage cholesterol column refer to esterified/free.
Size of RBC for comparison is 70,000 Å.

Representative Lipid Types

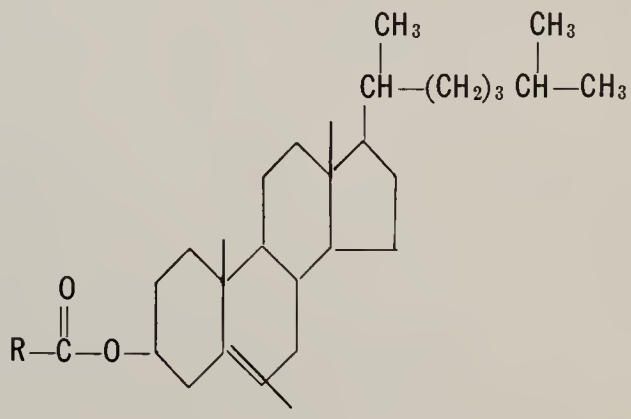
Triglyceride



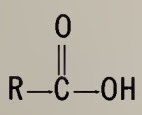
Phospholipid



Cholesterol Ester



Fatty Acid



The point which is sometimes confused is that when one speaks of triglyceride, cholesterol or phospholipids, high or low density lipoproteins, or α or β lipoproteins, he is speaking essentially of the same thing, differing only in ways of measurement. Fat gets from the gut to tissues in the form of the lowest density lipoproteins, the chylomicrons which are almost all triglyceride. These are formed in the gut wall during the process of fat absorption, travel up the thoracic duct and are dumped into the blood stream. They are cleared rapidly from the blood, however, by most tissues and are then stored or utilized for energy. An enzyme, lipoprotein lipase (clearing factor, LPL) apparently facilitates their transport into cells by hydrolyzing the contained triglyceride to glycerol and fatty acids, which then traverse the cell membrane.

In the fasting state, triglyceride is present in the blood in amounts normally of 50-150 mg/100 ml. This does not arise from the gut, obviously, and the level remains constant even during a prolonged fast. A small percentage (5-10%) of circulating FFA are re-esterified to triglyceride in the liver and secreted into the blood from whence they are then cleared by tissues. Whether lipoprotein lipase plays a role in this clearance is unclear. All circulating triglyceride is replaced in about 8-10 hours (turnover rate). Cholesterol and phospholipids are present in plasma in higher density lipoproteins in approximately equal amounts (150/250 mgm%) and tend to parallel each other in their rise or fall. Their function in plasma is not clearly understood. They arise largely in the liver (although most body tissues synthesize them locally also) and probably are being transported to sites of utilization. It has been speculated but not proven that they help in the transport of unsaturated fatty acids, since the fatty acids in their composition are largely unsaturated. It is also speculated that they may help to stabilize the lipoprotein particle. Cholesterol in plasma is about 75% esterified—i.e. a fatty acid is attached at the three position. The turnover rate of plasma cholesterol is considerably slower than that of triglyceride. Cholesterol injected into plasma equilibrates slowly with most body tissues except brain. The turnover time of the exchangeable body cholesterol pool is on the order of 75-100 days. Cholesterol excretion from the body is almost entirely in feces. Plasma free fatty acids (10-25 mgm%) as mentioned are on their way from fat tissue to sites of utilization as energy. They are thus turning over quite rapidly, the whole plasma pool being replaced about every 10 minutes.

HYPERLIPEMIAS

Hyperlipemic states may be described as either primarily hypertriglyceridemia or hypercholesterolemia or mixtures thereof. Hyperphospholipidemic states are not generally recognized as such because it is assumed that they are not pathologic but, as mentioned before, any state of hypercholesterolemia is accompanied by a concurrent hyperphospholipidemia.

Hypertriglyceridemia is accompanied by a visible cloudiness of the serum when the TG level rises above 300-400 mgm%. This is because of the presence of large amounts of the very low density lipoproteins (VLDLP) whose particles are large and scatter light. Hypercholesterolemia, on the other hand, without hypertriglyceridemia, is always accompanied by a clear serum.

Hypertriglyceridemia has been recently classified into two types—fat-induced and carbohydrate-induced. Fat-induced hypertriglyceridemia (hyperchylomicronemia) is a rare familial syndrome, apparently due to a deficiency of the enzyme, lipoprotein lipase. For this reason, they are unable to remove chylomicrons from their blood and have a prolonged lipemia following a fatty meal. Removal of fat from their diet controls the condition. The more common type of hypertriglyceridemia is the so-called carbohydrate-induced type. These patients are not deficient in lipoprotein lipase. They are so named because a low-fat, high carbohydrate diet aggra-

TABLE II—Types of Hyperlipemia

	TG	Chol	PL	Remarks
Fat Induced Hypertriglyceridemia	++++	—	—	Chylomicronemia. LPL deficient, Familial. Fat floats on top of plasma. Atherosclerosis not increased. Cloudy serum.
Carbohydrate Induced Lipemia	+++	++	++	VLDLP, not LPL deficient. Familial ±. Fat doesn't separate. Atherosclerosis increased. Skin xanthomata. Cloudy serum. Frequent insulin independent diabetes.
Hypercholesterolemia	+	++++	++++	Familial, LDLP, clear serum, tendon xanthomas, atherosclerosis increased.
Nephrotic Syndrome	++	+++	+++	VLD & LDLP, probably secondary to hypoalbuminemia. Increased atherosclerosis.
Biliary Cirrhosis	++	+++	++++	LDLP. Increased free cholesterol. Atherosclerosis not increased.
Hypothyroidism	+	+++	+++	Cholesterol production decreased. Atherosclerosis ± increased.

Number of + refer roughly to degree of elevation of plasma lipid type.

vates instead of correcting the condition. This type is frequently combined with hypercholesterolemia, and these patients apparently develop atherosclerosis at an accelerated rate, as do patients with pure hypercholesterolemia. There is frequently an associated insulin-independent diabetes. The condition arises probably as a consequence of deficient clearance of triglycerides in the VLDLP.[5] Hepatomegaly may be present due to accumulation of fat. The disorder tends to be familial and may occasionally be associated with recurrent attacks of pancreatitis. Eruptive xanthomata are frequently seen in the skin. The plasma cholesterol and phospholipids are frequently elevated also.

Hypertriglyceridemias which are not responsive to either a high-fat or high-carbohydrate diet have also been described. Hypercholesterolemia in a severe form is found as a familial trait. Hyperglyceridemia is usually absent. Tendon xanthomas are frequently present. Damaging atherosclerosis is frequently found at an early age. Diabetes mellitus is rarely associated. Hyperuricemia and cholelithiasis are sometimes found. Increased cholesterol production has not been found.

Biliary cirrhosis and the nephrotic syndrome frequently show both hyperglyceridemia and hypercholesterolemia, with the latter more prominent. Phospholipids are increased inordinately in biliary cirrhosis as is the percentage of free cholesterol. The hyperlipemia of the nephrotic syndrome disappears with the return of the serum albumin to normal. Biliary cirrhosis is not associated with increased atherosclerosis whereas the nephrotic syndrome apparently is.

Hypothyroidism presents the paradox of hypercholesterolemia in the face of a marked decrease of cholesterol production. Correction of the hypothyroid state usually promptly corrects the hypercholesterolemia. There seems to be some increase in atherosclerosis, but the frequency has not been clearly defined.

Hyperglyceridemia is seen in certain glycogen storage diseases and lipoatrophic diabetes probably on the basis of increased FFA mobilization.

DIABETES MELLITUS

While mild degrees of hypercholesterolemia and hypertriglyceridemia are seen frequently in diabetes mellitus, the severity is not such, apparently, to account for the marked increase in atherosclerosis seen. Occasionally, marked hypertriglyceridemia with moderate hypercholesterolemia are seen in diabetic acidosis, but this usually disappears as

the diabetes is brought under control. Albrink[6] has stated that the complications of diabetes are better correlated with hyperglyceridemia than hypercholesterolemia. Recently, it has been reported that atherosclerotic complications are also associated with mild degrees of glucose intolerance without overt diabetes. The authors[7] were unable to demonstrate this with an intravenous glucose tolerance test in a well-controlled study on a homogeneous population sample.

HYPOLIPEMIC STATES

Two somewhat rare syndromes have been described which are due to deficiencies of either low or high density lipoproteins. Low density lipoprotein deficiency (Bassen-Kornzweig syndrome) is associated with steatorrhea, atypical retinitis pigmentosa, diffuse alteration of the central nervous system and a characteristic thorny appearance of the red blood cells (acanthocytosis). All plasma lipids are somewhat low. There appears to be an inability of these patients to form chylomicrons.

High density lipoprotein deficiency (Tangier disease) is also rare and is associated with a syndrome of enlarged reddish orange tonsils, lymphadenopathy and hepatosplenomegaly. The significant chemical alteration is a manifold increase in concentration of tissue cholesterol, predominately in the esterified form. Plasma lipids are characterized by an increase of triglycerides and a marked decrease of cholesterol and phospholipids.

TREATMENT OF HYPERLIPEMIA

Hyperlipemia is usually asymptomatic and approach to treatment is largely determined by one's belief whether or not lowering plasma lipid levels will reduce the chances of the patient's developing an atherosclerotic complication. The ability to determine whether or not this is so is hampered by heretofore largely ineffective means of control, but progress is being made in the development of effective drug therapy. The situation has many parallels to the present approach to treatment of adult onset diabetes mellitus.

The treatments of hyperlipemia are legion. Dietary control of hypercholesterolemia is largely ineffective unless the diet is very closely supervised. One study has shown that by having the patient buy only foods that had been specially prepared for the study, there was some degree of control. Dietary control under usual conditions is largely ineffective unless the patient is fanatic in following a severely limited diet.

Drug therapy is more promising. Among the drugs used currently are thyroid hormone analogues, estrogens, androgens, nicotinic acid in large doses, anabolic steroids, and chlorophenoxyisobutyl ethyl ester (Atromid-S). The last is currently under investigation[8] and appears to be most promising, but is not the final solution. The drug appears to be non-toxic and without significant side effects and is moderately effective in lowering both triglyceride and cholesterol levels.

It is clear that many gaps remain in our knowledge of lipid metabolism but, with the advent of new biochemical techniques as well as new interest, the future looks hopeful.

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REVIEW ARTICLE

BIOENGINEERING:
A definition by examples of the interaction between the engineering sciences and biology and medicine.

LAWRENCE STARK, M.D.[1]

Bioengineering, or Biomedical Engineering, is that field which deals with the interaction between the engineering sciences and biology and medicine. Because engineering is really two fields—*building* using scientific principles and *analysis* of complex mechanisms—bioengineering also is two fields: one having to do with building devices, the development of instrumentation and data processing systems; and the other the analysis of complex biological systems by means of the application of engineering sciences. At the present time biomedical engineering is experiencing a rapid and vigorous developmental phase in many universities throughout the country; especially those that are in the forefront of scientific and engineering teaching. It is, however, more convenient to divide bioengineering into five fields: two in which analysis predominates; two in which building instruments or systems predominates; and the fifth dealing with the special educational and teaching aspects of biomedical engineering.

1. *Cybernetics.* Cybernetics defined by Norbert Wiener is the science of control and communication in animals and machines.[1] It is in this first area of bioengineering that the most exciting scientific contributions have developed. Of biological control systems, the cardiovascular system is one of the most important. It has many complex properties such as distributed transmission line elements as well as complex mechanical constraints. The endocrine system which has important relationships to both metabolic control and the central nervous system unfortunately presents experimental difficulties in isolating and measuring components and variables. Neurological control systems, on the other hand, often conform to such important systems analysis requirements as undirectional transmission between casually related lumpedparameter elements. By this we mean that information passes undirectionally, undisturbed by backward interaction from one block to the next and that each block in the block diagram represents an operation or mathematical transformation that can be considered as being located at a node or in one point, that is lumped, rather than spread over real physical dimensions. A classical example of a neurological control system is the pupillary servo mechanism. Here the feedback path can be experimentally opened using either optical or electronic techniques. Both linear transfer function analysis including stability, oscillations and noise, and the application of sophisticated nonlinear engineering theory such as Wiener G-functional analysis has been successfully applied. Figure 1 shows the Nyquist

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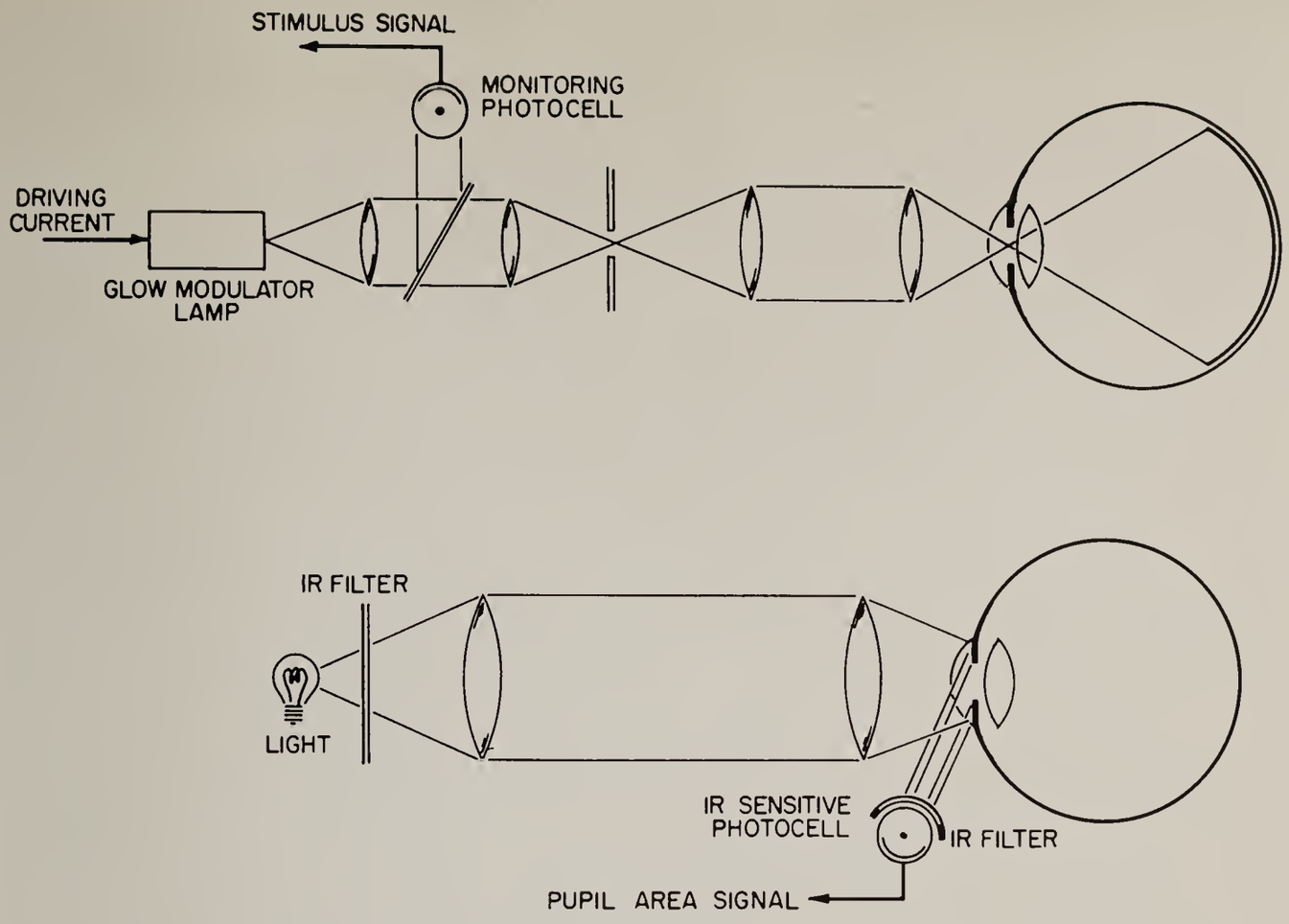

Fig. 1.—Sketch of a pupillometer.

diagram of the normal human pupillary system. Study of other neurological control systems such as hand and eye movement have shown these to be more complex than the pupil having properties of sample-data control systems as well as having input signal predictive operators which make them highly adaptive.[3]

The nervous system is also amenable to analysis in terms of information theory. An interesting example is the use of Claude Shannon's information theory to analyze the nerve impulse code in the simple crayfish tail light receptor system.[4] Figure 2 shows an example of an auto- and cross-correlation study which allows the information rate of three bits per second to be experimentally demonstrated by defining certain stochastic relationships between the nerve impulse trains. The lower two diagrams in Figure 2 show the interval histograms of the two photosensitive fibers, F_1 & F_2, carrying the same information concerning the light stimulation. These and the middle two diagrams, or autocorrelation functions, $\varnothing F_1F_1$ & $\varnothing F_2F_2$, show the nerve impulse trains to be quasiperiodic sequences. The upper diagram shows the cross-correlation, $\varnothing F_1F_2$, between the impulse trains in the two fibers. This is random, lying within the two standard deviation limits, and demonstrates absence of impulse interval correlation between the two fibers. The nerve impulse code thus is suggested to be an average frequency code transmitting 3 bits/second, rather than a more precise interval code transmitting 100 bits/second. A bit is a simple binary, yes or no, piece of information.

2. *Bionics*, or as Professor McCulloch prefers—biomimetics—has been defined by Steele of the Air Force as the utilization of principles of design of biological systems for the construction of man-made

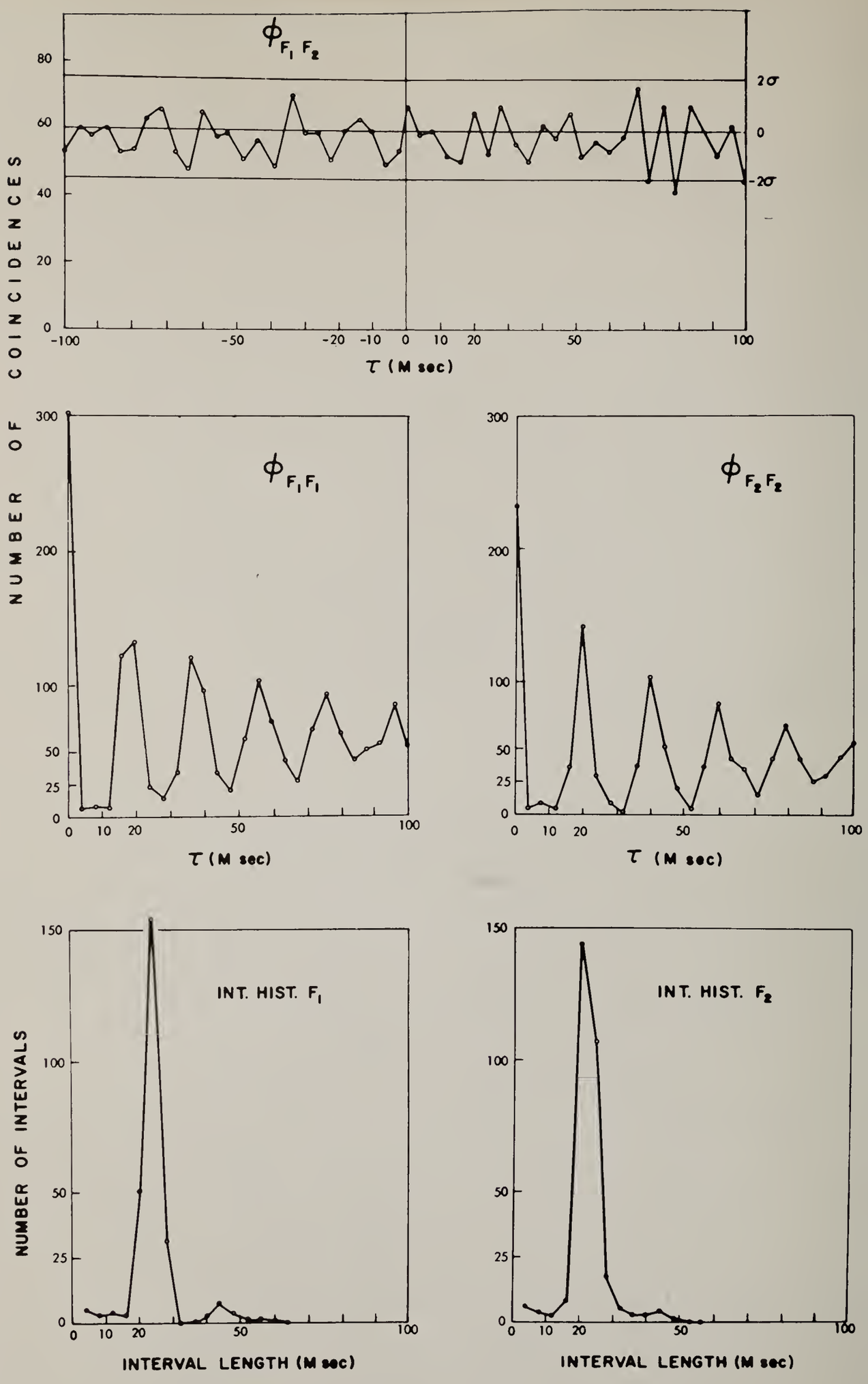

Fig. 2.—Absence of correlation; periodic signals during light stimulation.

devices. One of the most exciting developments in this field occurred in middle "40's" when Von Neumann, Goldstine, Bigelow and Burks utilized McCulloch-Pitts neurons to design the Institute for Advanced Study digital computer. McCulloch and Pitts had developed the formal neuron as a "poverty stricken" example abstracted from the richness of normal brain neurons, in order to analyze in terms of Boolean algebra the properties of networks of such neurons.[5]

Von Neumann, in carrying out the logical design of this digital computer in which logical design was separated in principle from hardware design, used McCulloch-Pitts neurons to draw his logical diagrams as shown in Figure 3.[6] The names given to various portions of the computer such as the memory organ and the logical organ are other more intuitive examples of the application of principles of design of biological systems to the construction of an important artificial device.

ADDER

DISCRIMINATOR

MULTIPLIER

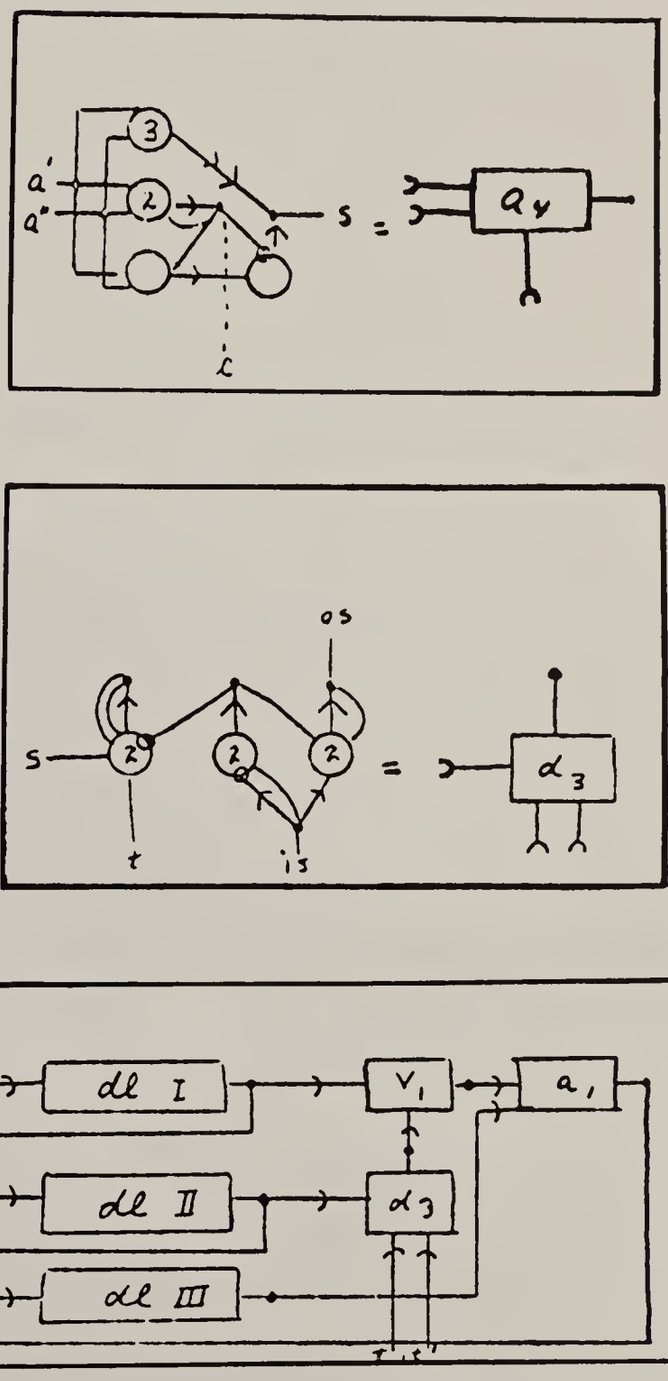

Fig. 3.—Logical design of EDVAC Computer elements using McCulloch-Pitts neurons from *First Draft of a Report on the EDVAC* by John von Neumann, June 30, 1945; Contract No. W-670-ORD-4926, Between the United States Army Ordnance Department and the University of Pennsylvania.

Other areas of importance in biomimetics are recent developments of artificial robots such as those designed to operate in lunar environments utilizing principles of postural and manual control, as elucidated in human engineering studies. Another exciting area is the development of artificial intelligence pattern recognition devices for visual pattern recognition in the directions both of hardware devices and also of digital computers. An example of the latter is the artificial intelligence program for pattern recognition analysis of electrocardiograms which will be described later.

General features of pattern recognition now appear to be grouped in three

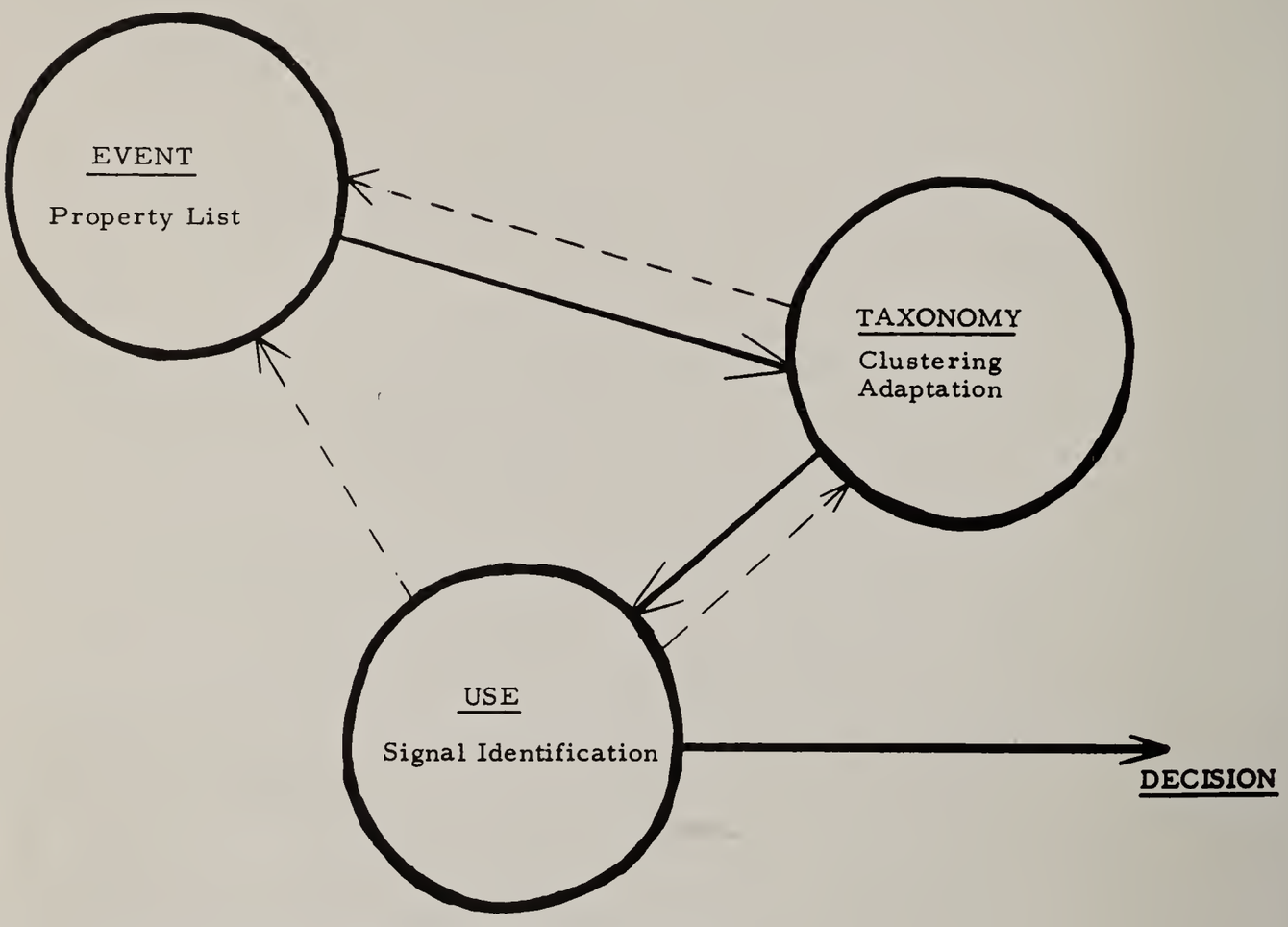

Fig. 4.—General features of pattern recognition research.

problem areas as shown in Figure 4.[7] First is the problem of the selection and measurement of properties of an event or object to be recognized. The sum total of these properties and their scale of measurements constitutes the reality of an event. Each event thus is transformed into a point in N-dimensional property space. If certain events occur repetitively and cluster in a particular region of this property space, they will be recognized as similar; other events clustering in distant areas will be recognized as dissimilar. Another of the problems in building a self-adaptive or self-organizing pattern recognition device or program is to make appropriate decision rules for partitioning the space appropriately to create a taxonomy. The third problem area is the use of this categorized space or taxonomic classification for some purpose such as signal identification. This bionic pattern recognizer leads us naturally to biomedical engineering instrumentation.

3. *Instrumentation* as an important field of Biomedical Engineering must, first of all, deal with the development of transducers. These are devices that either measure some physical quantity and

transform it into a convenient amplified electrical signal voltage, or they control the level of a particular environmental physical quantity according to a control voltage signal. The pupillometer shown in Figure 5 is an example of such a transducer instrument.[2] Because it is designed to be used in input and output analysis studies, it has two paths. The first is an input path whereby the physical stimulus, light, is dynamically controlled by an electrical voltage generated by a function generator or by an online computer organizing the experiment. The second path is the response measurement path whereby an infra-red reflection is used to measure the size of the pupil. Here the measurement system transduces the amount of infra red light into an electrical voltage which is a measure of pupillary area. This is then sent to a pen recorder or into the digital computer for subsequent analysis.

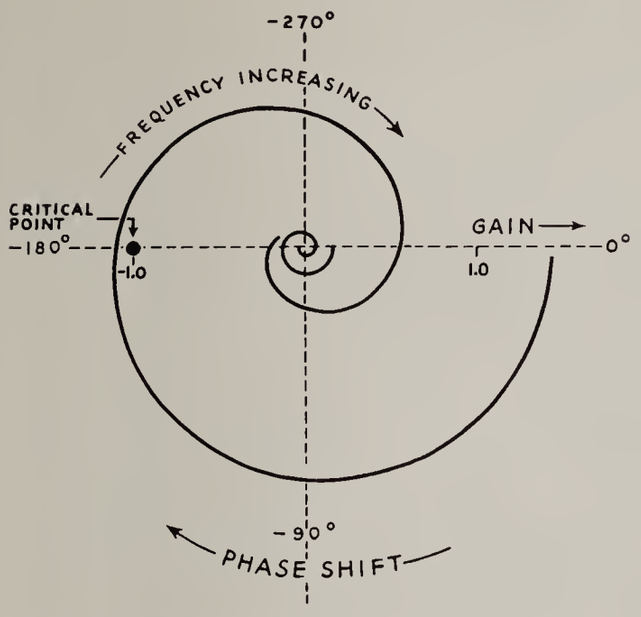

Fig. 5.—Nyquist Diagram of Pupillary Response.

Oftentimes exceedingly complex special transducers are invented by bioengineers, such as the new ultrasound visualization system developed by Professor John Jacobs at Northwestern University which is shown in Figure 6.[8] This device provides a dual transducer for generating ultrasonic energy and sending it into the biological tissue, and as well sensing the reflected ultrasound energy and displaying it as a visual picture on the quartz plate of the transducer. This new system may one day rival x-rays as a means of looking into biological systems.

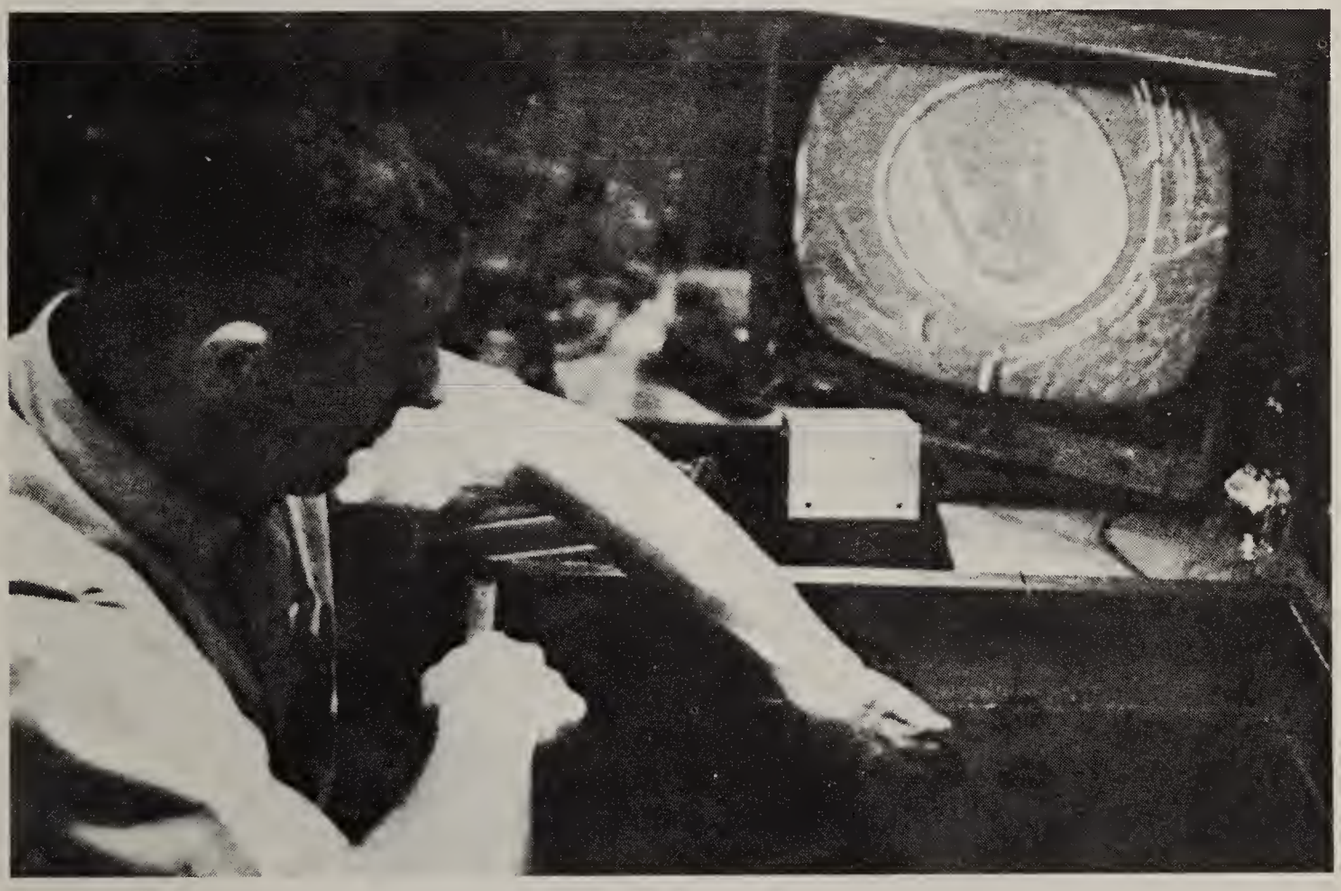

Fig. 6.—New ultra sound visualization system.

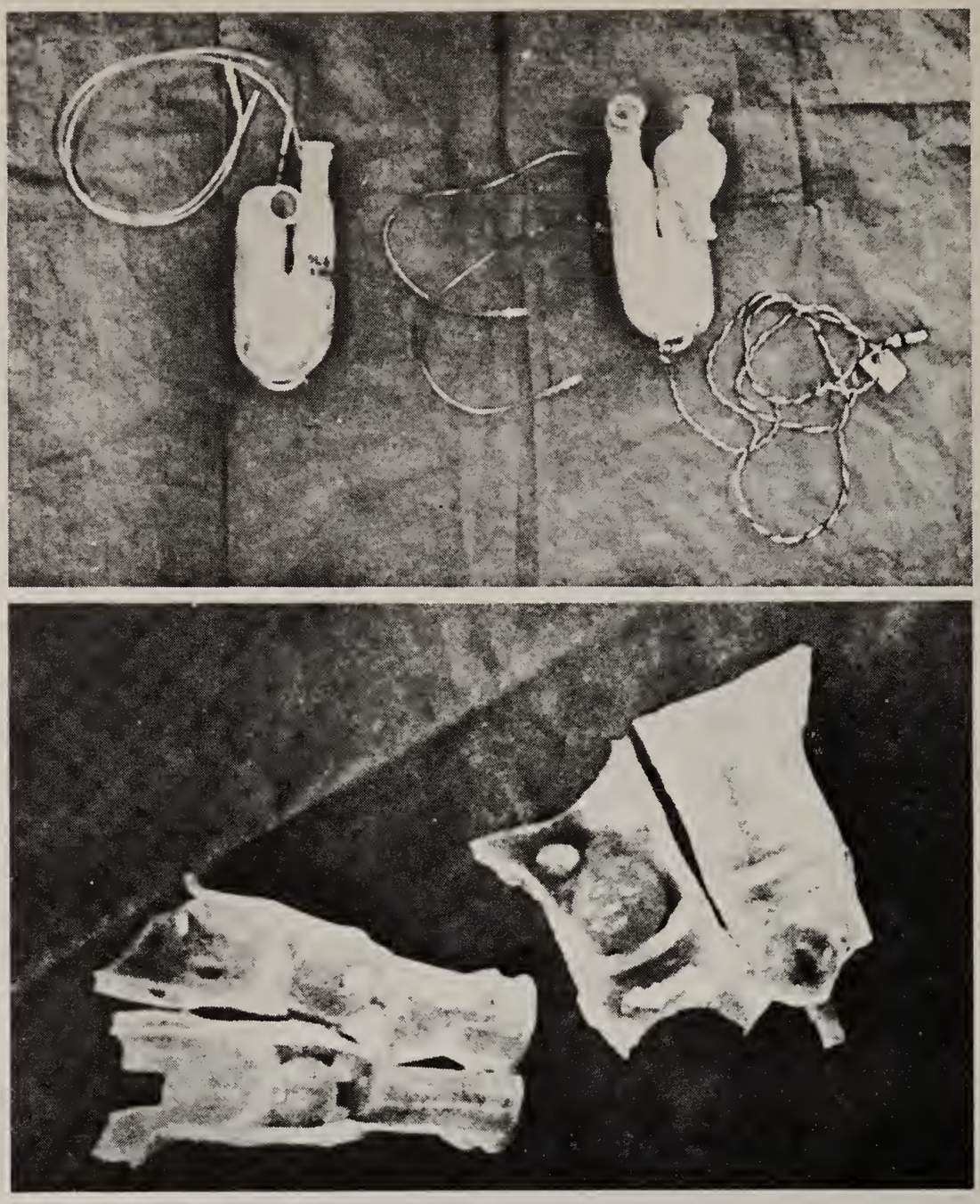

Fig. 7.—Artificial heart. Left and right plastic hearts (a) show openings to left atrium and aorta on left heart; pulmonary artery, superior and inferior vena cava on right heart. Plastic tubes serve as pressure taps, wires are leads from position coils implanted in ventricle walls. Cross-section (b) reveals ball valves; plastic studs replace usual cage.

Prosthetic devices are another example of biomedical engineering instrumentation. In addition to well-known artificial hands and their modern electronically controlled counterparts, even internal organs of the body, such as the kidney and the heart are now being replaced by prosthetic devices. The artificial kidney, of course, is still too large to be inserted within the human body and the patient must be attached to the dialysis apparatus intermittently during his illness. In Figure 7 are shown plastic hearts that are now being inserted into calves and may soon be used for humans. These developments are occupying the attention of many people throughout the Biomedical Engineering world and the particular illustration seen in Figure 7 was selected from the work of Professor Kolff, a recognized pioneer in this area.[9]

More complex instrumentation systems such as complete control of heart-lung machines, anesthesia, and physiological monitoring systems for a modern operating room also fall into the general area of instrumentation and lead us to consideration of the digital computer.

The high-speed digital computer is becoming a universal mathematical and logical tool for complex instrumentation systems. Together with modern communications and accessory analog computers they can be used to control, design and edit an actual experiment as shown in Figure 8 wherein the capsuled computer system is illustrated.[10] Here we see that the physician or Bioengineering experimental scientist has in his own laboratory effectively all the facilities of the digital computer to control and display experimental variables in an online remote configuration. Among the most exciting features of digital computers, however, is not their numerical or arithmetic abilities, but their logical properties.

Non-numerical uses of computers that have recently become widely known have mainly been interesting demonstrations such as the checker-playing program of Professor Samuel to illustrate the ability of the computer to develop tactical and strategical principles in game playing.[11] Language translation is also a good example of non-numerical use of digital computer. We are all familiar with the alien mistakes of a computer such as translating from the English, "The spirit is willing but the flesh is weak," to the Russian, "The vodka is good but the meat is bad." This example, of course, stresses the differences between human and artificial intelligence.[12] However, the artificial intelligence electrocardiographic diagnostic program has been used as a model of human brain processes. Careful analysis of the way in which doctors pattern-recognize electrocardiograms and the way the computer classifies in its self-organizing mode may lead scientists into general methematical concepts of central nervous system activity. In Figure 9 is a sample of the output of the computer electrocardiographic diagnostic program which shows, indeed, how similar it is to the human cardiologist. Not only do the apparent features of the computer diagnoses correspond closely to the human ones, but even such fine characteristics as the amount of variability or statistical fluctuation in repetitive diagnostic trials has been shown to have

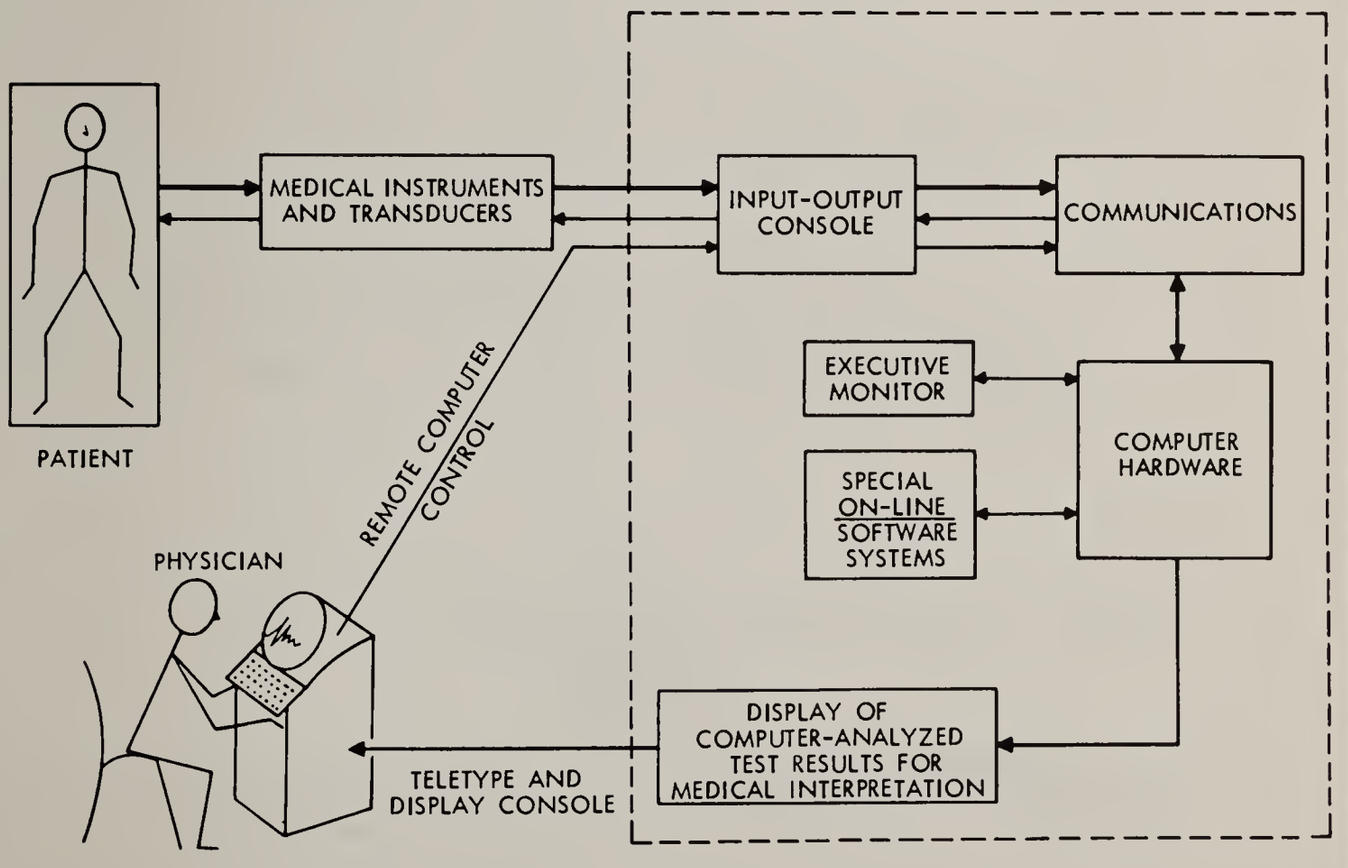

Fig. 8.—Capsuled Computer System.

similar properties in detailed comparison experiments between the computer and humans.[7]

4. *Information systems* in bioengineering are ultimately related to the exploitation of properties of digital computers. The hospital information system research area is now being actively developed by several universities, hospitals and computer companies. Here the information, materials, and personnel of a hospital are communicated, transported, and scheduled so as to make for maximum use of scarce facilities such as X-ray rooms and operating theaters as well as to provide maximum comfort and flexibility for both patients and hospital staff. Accessory information derived from laboratory studies of epidemiological results, information retrival of patient records, and more rational accounting systems are all part of the general hospital information system. Medlars is an on-going system developed by several engineering companies working with the National Medical Library which now indexes all of medical literature and makes it more rapidly available to the medical world.

Man-machine systems have attracted the attention of the people of our country in terms of astronauts flying space ships around the earth and eventually to the moon and to Mars. Here the problem of

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NAME      ALICE LEARY
HOSP. IDENT. NO. 127645

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1.   TENTATIVE INTERPRETATION

       A. RHYTHM ANALYSIS
            VENTRICULAR PREMATURE BEAT WITH COMPENSATORY PAUSE
            1 IN 16

       B. AMPLITUDES AND TIME INTERVALS
            HEART RATE 82
            AMPLITUDES  MV
                ST SEGMENT 0.03  0.04  0.08
                P  0.12  Q -0.06  R 1.34  S -0.37  T 0.38
            DURATIONS  SEC
               P  0.11  QRS 0.11  PQ 0.16  QT  0.38

       C. PATTERN INTERPRETATION WITH CORRELATION COEFFICIENT
            P PULMONALE 0.36
            INCOMPLETE RIGHT BUNDLE  BRANCH BLOCK 0.84
            NORMAL T WAVE 0.63


11.  ELECTROCARDIOGRAPHIC INTERPRETATION

        NORMAL HEART RATE  82 PER MIN.
        VENTRICULAR PREMATURE BE   WITH COMPENSATORY PAUSE 1 IN 16
        INCOMPLETE RIGHT BUNDLE BRANCH BLOCK


111. ELECTROCARDIOGRAPHIC DIAGNOSIS
        VENTRICULAR PREMATURE BEATS WITH COMPENSATORY PAUSE 1 IN 16
        UNCOMPLICATED INCOMPLETE RIGHT BUNDLE BRANCH BLOCK
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Fig. 9.—Sample of the output of the computer electrocardiographic diagnostic program.

environmental control in outer space is emphasized with the obvious dangers of low pressure, radiation, and of violent fluctuations in temperature and light. Taken with the changes in gravitational force, these difficulties make a very complex environmental control system necessary if people are to live aboard these space ships.

From this point of view, our planet earth is a space ship for us all. Especially in crowded situations such as cities, the as yet ineffective control of our air and water supplies and the disposition of our sewage and other effluents makes the problem of the "metabolism of the city" and indeed of our entire civilization an important one. Such traffic flows as automobiles and mail throughout our society are another aspect of a complex man-machine system, and may fall within the area of bioengineering.

5. *Education, Teaching, Training and Re-education* are all important in our increasingly technological and scientific society. At the present time, the medical world is in a crisis. The developments in mathematics, physics and engineering sciences have gone too fast, for not only the general practitioners and the medical student to keep pace with, but have left behind in serious fashion, the members of the academic medical faculties. For this reason, such important institutions as the National Institute of Health in Washington is turning increasing attention to the continuing scientific development of the medical scientist with re-education of senior medical faculty personnel who have already demonstrated creative ability in their fields. Here, re-education in terms of biomathematics, physics, and engineering is necessary. The Bioengineering Program in many universities is intimately related with these developments in education. Conversely, the problem of engineering education, with increasing attention given to complex mathematical analyses, is to find interesting real systems of enough complexity to test modern theories. Many engineers who are not particularly interested in Bioengineering find it useful to do their doctoral thesis work or even undergraduate and graduate projects in the life science field because of the severe test that the life sciences place on the application of engineering principles. Thus, there exists clear utility for Bioengineering as schooling grounds for these engineering science principles.

A hopeful side of biomedical engineering training is that with the development of systems sciences such as control and communications and information, it looks as if all the sciences are coming closer and becoming more unified. All sciences use input and output descriptions, studies of materials, energy conversion principles, and share common tools, such as analog and digital computers for model building. In this way, the unity of the descriptive sciences—physics, chemistry, biology, sociology, psychology—is becoming clearer as they share more and more the common structure of systems science.

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ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

Injuries to the Clavicle with Neurovascular Complications. F. M. Howard and S. J. Shafer: *Journal of Bone and Joint Surgery, 47A:7, 1335–1346, Oct., 1965.*

There were fourteen cases presented illustrating that compression of the neurovascular structures generally occur at two different regions of the clavicle and the symptoms vary at these levels:

1. Compression by the sternal end of the clavicle with posterior displacement can obstruct the carotid artery and produce symptoms of syncope.
2. Compression at the inner and middle third of the clavicle by depression of the lateral fragment can obstruct the subclavian vessels or impinge on the brachial plexus.

Adequate space between the clavicle and the first rib must be insured for the passage of the subclavian vessels and brachial plexus from the thoracic outlet. The surgical implications are discussed.

Fractures of the Apophyses in Adolescent Athletes. F. M. Howard and R. J. Piha: *Jour. of Amer. Med. Assoc., 192:10, 842–844, June 7, 1965 and Modern Medicine, 33:18, 144, Aug. 30, 1965.*

Eight apophyseal fractures occurred in six adolescent male athletes. All of the fractures occurred by violent muscle contraction while the athletes were engaged in vigorous sports. Closed reduction generally gave satisfactory results except with marked displacement of the apophysis of the ischial tuberosity and tibial tubercle.

Preparation of Fluorescein Isothiocyanate-Labeled Gamma Globulin by Dialysis, Gel Tiltration, and Ion-Exchange Chromatography in Combination. R. E. Dedmon, A. W. Holmes and F. Deinhardt: *Journal of Bacteriology, 89:3, 734-740, 1965.*

Antiviral immune gamma globulins isolated from rabbit and guinea pig sera were labeled through dialysis membranes with fluorescein isothiocyanate and purified in several ways to eliminate nonspecific staining. Gel filtration of the conjugate with Sephadex G-25 coarse beads followed by column fractionation with diethylaminoethyl-Sephadex yielded consistently highly specific staining materials. Fluorescein-protein ratios varied between 1.0 and 4.0. This technique has proved to be simple and reliable, and is less time-consuming than previous techniques.

Fibrositis. E. F. Traut: *Med. Clin. of N. Amer., 49:1, 151, Jan., 1965.*

Rheumatic complaints and findings in the soft tissues attached to the skeleton are encountered daily. Considerable, even acrimonious, disagreement exists in the semantics of their diagnosis. Lacking consistent histologic patterns their very existence is debated. Although not threatening to life they disturb to a varying degree and often in an episodic manner the joie de vivre. These forms of nonarticular rheumatism have been best treated with heat, massage, muscle re-education, obesity control and improved mental and physical hygiene. Increased rest and lessened emotional reaction to environmental stresses are rewarding in most cases.

Drugs have not given notable or sustained relief.

Cultists know well the often immediate relief obtainable by skillful manipulation of contracted, stiff spines or extremities. Physicians can acquire this ability thus avoiding the embarrassment of having a salicylate-saturated client suddenly recover after an "adjustment". Infiltration of trigger points with procaine, with or without an accompanying injected steroid, offers another satisfactory approach to this common cause of pain and disability.

Serum Proteins in Cervical Mucus. E. K. Straus, G. F. B. Schumacher, and G. L. Wied: *Amer. J. Obstet. Gynec., 91:1035-1049, 1965.*

Increase of leukocytes in the cervical mucus of patients with localized pathological changes is associated with variations in the immunoelectrophoretic pattern. Normal pattern, however, is not significantly altered by menstrual cycling, hormonal therapy, or use of contra-

ceptives. Immunoelectrophoretic analysis reveals the number of protein fractions, immunoelectrophoretic analysis reveals the number of protein fractions, immunologically related to serum proteins, being excreted with the mucoid substance. With specific antiserums and special staining, individual serum proteins can be identified. In healthy women, albumin, transferrin, and 7S-gamma globulins are normally present, along with alpha-2 antitrypsin and prealbumin in more than one-half. In women with cervical erosion, cervicitis, or pelvic inflammatory disease, more precipitin lines occur, and benzidine reaction, indicating presence of haptoglobin, is usually positive.

Of 42 specimens of cervical mucus studied, 21 were from apparently well women at different stages of the menstrual cycle, 8 from patients receiving norethynodrel with mestranol (Enovid®) as an oral contraceptive, and 12 from women with localized pathological changes. The electrophoretic pattern of a 39-year-old surgically castrated woman with histologically proved carcinoma in situ remained unchanged after administration of diethylstilbestrol and medroxyprogesterone (Provera®), despite alterations in the cytological pattern.

Clinical Pathological Conference. H. Battifora, M. S. Rosenberg, M. L. Bogdonoff, and M. Weinberg, Jr.: *American Heart Journal, 69:6, June 1965.*

A 23 year old man with a history of congenital heart disease and with progressively increasing dyspnea was discussed in this C.P.C. held at Presbyterian-St. Luke's Hospital. The cardiac catheterization data, particularly the presence of a pulmonary diastolic pressure of 24 mm Hg. with a systolic pressure of 74 mm Hg. was considered suggestive of peripheral stenosis of pulmonary arteries. The radiologic findings confirmed such diagnosis by showing multiple occlusions of the pulmonary vasculature in an angiogram. Findings at autopsy revealed several areas of congenital stenosis with post-stenotic dilatation and secondary parenchymal changes. The current surgical approach was discussed by Dr. Weinberg.

Electron Microscopy and Tritiated Thymidine in Gradation of Malignancy of Human Bladder Carcinomas. H. A. Battifora, R. Eisenstein, H. H. Sky-Peck and J. H. McDonald: *J. Urol., 93,* Feb., *1965.*

A good correlation was found between the percentage of cell nuclei labelled with tritiated thymidine and histologic grading of malignancy in human bladder cancer. Electron microscopy of these tumors also shows a continuous gradation of change from the normal as the grade of malignancy increases. Although there were no specific changes seen in the electron microscope alterations from normal included increased numbers, size and complexity of nucleoli, variability in nuclear shape and size, increased nuclear chromatin and increased complexity of the cytoplasm. Foci of squamous metaplasia were occasionally encountered in tumors that were histologically transitional cell in type. The more malignant tumors contained large autophagic type vacuoles in relation to areas of necrosis. No changes from the normal were found, either by radioautography or electron microscopy, in bladders bearing tumors when biopsies were taken from the non-tumor bearing areas.

Pupillary Response of the Screech Owl, Otus asio. L. G. Bishop and L. Stark: *Science, 148:3678, 1750-1752, June 1965.*

Abstract. The latent period of constriction in the owl is only half that in the human, and the latent period of dilatation is about equal to that in the human. Similarly, the rise time of constriction in the owl is much faster than that in the human. The owl system has the characteristics of a low-band-pass filter. The owl's frequency response is over an octave lower than that of the human, but its phase lags are shorter.

Post-Heparin Phospholipase and Fatty Acid Transesterification in Human Plasma. C. Vogel, G. Ryan, J. L. Koppel and J. H. Olwin: *J. Lipid Research 6: 335-340, 1965.*

The site of action of a previously described human post-heparin plasma phospholipase on phosphatidyl ethanolamine has been explored in conjunction with the finding of a fatty acid transesterification activity is post-heparin plasma. Fatty acid esters of methanol, ethanol, or glycerol were formed when these alcohols were appropriately added to incubation mixtures of phosphatidyl ethanolamine and post-heparin plasma. The fatty acids of this transesterification reaction were derived from the degradation of phosphatidyl ethanolamine to lysophosphatidyl ethanolamine. The data obtained indicate that, in contrast to

the site of action of venom or human pancreatic phospholipase A, the post-heparin plasma phospholipase and transesterification activity involve the fatty acid at the 1-position (alpha-position) of egg phosphatidyl ethanolamine.

Phospholipid-Protein Interactions in the Formation of Prothrombin Activator. E. R. Cole, J. L. Koppel and J. H. Olwin: *Thromb. Diath. Haem. 14:431-444, 1965.*
It was found that complete prothrombin activators could be formed by first preparing an asolectin-calcium-autoprothrombin C complex and then reacting this complex with Ac-globulin. A small amount of the resulting product was very effective as an activator of purified prothrombin without further addition of calcium or any other cofactor. If the autoprothrombin C preparation used to prepare the complex was free of traces of prothrombin, the complete activator was stable for several hours at room temperature. Stable preparations of the complete activator were centrifuged, resulting in the sedimentation of most of the activity. Experimental evidence indicates that activator activity is highest when autoprothrombin C and Ac-globulin are complexed to the same phospholipid micelle, rather than when the two clotting factors are complexed to separate micelles. These data suggest that the *in vivo* prothrombin activator may be a sedimentable complex composed of a thromboplastic enzyme, calcium, Ac-globulin and phospholipid.

Bleeding After Renal Biopsy in Pregnancy. L. J. Schewitz, I. A. Friedman, and V. E. Pollak: *Obstet. Gynec., 26, 295-304, 1965.*
Following 90 needle renal biopsies during or soon after pregnancy, the incidence of hemorrhagic complications was 18.9 per cent; following 450 biopsies in non-pregnant patients the incidence in our laboratories was only 6.2 per cent. Four patients (in the pregnancy series) developed perirenal hematomas. One of these died of cardiac arrest immediately after surgery to stop the bleeding, and a second had nephrectomy for a ruptured renal pelvis which occurred after 23 days of severe hematuria. Two other patients had severe hematuria for 14 and 6 days. In the remainder of the patients the complications were of lesser severity.

Two of the patients with prolonged hematuria were found to have coagulation and bleeding mechanism defects after the biopsies, although no abnormality had been detected before the biopsies.

Our findings suggest that this high incidence of complications is related to one or more of the following factors: 1. Passage of the biopsy needle into the renal medulla or into the renal pelvis. Renal medulla was found in the biopsy material of 14 of the patients with complications. 2. The presence of hypertension and arteriolar sclerosis may predispose to bleeding. Both factors were present in a majority of our patients. 3. Toxemia of pregnancy may cause coagulation and bleeding defects.

We recommend great caution in the use of renal biopsy during pregnancy.

Vascular Injuries Associated with Fractures. G. de Takats: *Chicago Medicine, 68:12, June 1965.*
Anyone interested in the immediate care of fractures must be aware of possible injuries to arteries, veins and lymphatics. The injury may occur at the time of the fracture, during open or closed reduction or as a late consequence of callus-pressure or deep venous thrombosis. In addition to the repair of indispensable arteries or veins, ligation of these structures is often useful. Splitting the deep fascia in the presence of increasing edema or hematoma formation adequately decompresses the injured vascular segments. Some examples of vascular injuries associated with fractures have been given in more detail.

Dynamics of Plasma Triglyceride Turnover in Man. W. G. Ryan and T. B. Schwartz: *Metabolism 14:12, 1243-1254, Dec., 1965.*
Plasma free fatty acid (FFA) and triglyceride (TG) influx rates were determined in 17 patients with a wide range of plasma triglyceride levels. No significant correlation was found between plasma FFA or TG influx rates and the plasma TG level in these patients. Alterations in the plasma TG levels were induced by various treatments, but plasma TG influx rates were not significantly or concordantly changed. It is concluded that plasma FFA and TG influx rates do not exert primary control of plasma TG levels. Rather, the data are compatible with the thesis that TG *clearance* is a major determinant of plasma TG concentration.

Epidemiology and Etiology of Viral Hepatitis (Chapter 22). F. Deinhardt and A. W. Holmes: *Progress in Liver Diseases, H. Popper and F. Schaffner, Editors, 1965.*
A review article, summarizing and critically analyzing the current knowledge of the epidemiology and etiology of viral hepatitis, including proposals for new approaches to the study of the etiology of hepatitis.

Virus Susceptibility of Marmoset Kidney Cell Cultures. A. Schur and A. W. Holmes: *Proceedings of the Society for Experimental Biology and Medicine, 119, 950-952, 1965.*
Attempts were made to infect primary marmoset kidney cell cultures with 28 different agents representing the major groups of viruses. Although variable evidence for myxovirus multiplication was obtained and poliovirus type II strain LEON multiplied without cytopathology, this type of cell culture proves susceptible to a variety of other agents.

An Electron Microscope and Cytochemical Study of Adenovirus in Colchicine-Induced Micronucleated, Tissue-Cultured Cells. T. J. Starr, M. Kajimi and A. W. Holmes: *Texas Reports on Biology and Medicine, 23:3, 607-620, Fall 1965.*
Cytochemical staining procedures were used to visualize the chromosomal changes associated with the formation of colchicine-induced, micronucleated, tissue-cultured cells. The sequence of events involved a condensation of the metaphase chromosomes and subsequent formation of membranes. Micronucleated cells were challenged with cytoplasmic and intranuclear viruses. As demonstrated by acridine orange staining and electron microscopy, a morphologically intact nucleus was not a prerequisite for virus maturation. In view of the structural and associated functional aberrations of the micronucleated cell, this cell-type is presented as a novel environment for study of host-parasite interactions.

Left Atrial Contribution to Ventricular Performance in Mitral Stenosis. R. A. Carleton, M. Passovoy, and J. S. Graettinger: *Circulation 32:64, 1965.*
Previous observations in patients with mitral valvular disease, which showed insignificant increases in cardiac output when atrial fibrillation was converted to sinus rhythm, suggested that left atrial systole made only a small contribution. Two groups of patients were studied at various paced ventricular rates (VR): 12 with heart block without valvular disease (42 paced rates) and 3 with mitral stenosis (6 paced rates; mitral areas less than 1.1 cm^2). Since average peak aortic systolic pressure correlated highly with average stroke output (Fick) in patients studied at more than 3 VR, peak aortic systolic pressure (PASP) was used as an index of beat-to-beat changes in stroke output. A parabolic relationship between PASP and P-R at each VR permitted statistical estimation of each optimal P-R interval at which PASP was highest. The least effective P-R intervals were those at which PASP was lowest. Optimal P-R was inversely related to VR ($r = -0.89$).

In the 12 patients, atrial contribution, expressed as the percentage increment of PASP at each optimal P-R above the lowest PASP values, was significantly related to VR ($r = +0.79$); at rates of 35 to 59, the contribution was $8.9 \pm_{SE} 1.3\%$; at 60 to 89, $18.9 \pm 1.6\%$; and at 90 to 125, $26.8 \pm 2.2\%$. Two patients with mitral stenosis, studied at a VR of 100, had atrial contributions of only 7 and 11%. The third, studied at VR of 60, 80, 97, and 120, had no atrial contribution above 12%. Mitral stenosis significantly reduced left atrial systolic effectiveness ($P < 0.01$) and the hemo-dynamic importance of sinus rhythm.

Implementing Improvements in an Outpatient Department. W. R. Tucker, I. R. Turner, J. C. Lashof, N. W. Ream, and J. J. Herman: *Archives of Environmental Health, 11, 22-27, July 1965.*
A study assessing the value of a periodic examination of ambulatory patients in an outpatient clinic was begun at Presbyterian-St. Luke's Health Center in 1962. It became apparent during the course of that Study that the outpatient clinic itself required periodic review. The evaluation subsequently undertaken led to changes and innovations in the following areas: (1) establishment of a quality control unit; (2) broadening the scope of a new patient work-up; (3) instituting periodic physical examinations for patients in the medicine clinics; (4) coordination of services in the management of the patient; (5) medical student assignments; (6) establishment of a diagnostic index; (7) the establishment of a quarterly chart review by the physicians and students; (8) the design of a mechanical system for the storage of medical and financial information; and (9) the design of a medical care check list.

It was not possible to document improvement in the level of medical care as a result of these innovations. This may be due in part to our inability to accurately define and measure the level of medical care. However, it was felt that such measures can lead to improvements in medical care.

Atrial Contribution to Ventricular Performance. R. A. Carleton and J. S. Graettinger: *J. Clin. Invest., 44, 1033-1034, 1965.*

This study of human atrial function was prompted by the observation that cardiac output did not increase in patients converted from atrial fibrillation to sinus rhythm if their ventricular rates (VR) were below 100 per minute. Ventricular pacing was performed in 12 patients with complete A-V block during hemodynamic studies. The intervals between sinus node-induced atrial systoles and pacemaker-stimulated ventricular systoles varied randomly and were estimated from the P-R intervals in the electrocardiograms. At any VR (35 to 125), the average of peak aortic systolic pressure (PASP) was significantly related to average stroke output (Fick); therefore changes in PASP were used as the index of beat-to-beat changes in stroke output. Scattergrams of PASP as a function of P-R at each rate appeared parabolic; PASP was lowest at very short or very long P-R and highest at an intermediate P-R. The P-R corresponding to the highest PASP, at which the maximal atrial contribution occurred, was defined as the optimal P-R; it was computed by least squares parabolic regression analysis for each of the 34 scattergrams. These optimal P-R were inversely related to VR ($r = -0.89$). At rates under 60 they were over 0.21 second; at rates over 90 they were under 0.19 second. This change in optimal P-R approximates the physiologic change in P-R with rate. The magnitude of atrial contribution was expressed as the percentage increment of PASP, at each optimal P-R, above the lowest PASP values. These maximal contributions were also significantly rate related ($r = +0.79$); at VR 35 to 59, 9.8% (SE $\pm$1.3%); at 60 to 89, 18.1% ($\pm$1.7%); and at 90 to 125, 27.4% ($\pm$2.9%). These results suggest that, although atrial systole is of relatively little importance at slower VR, both the occurrence and timing of atrial systole become increasingly important at higher heart rates.

Oxford Survey of Childhood Cancers, Progress Report III: Leukaemia and Down's Syndrome. J. C. Lashof and A. Stewart: *Monthly Bulletin of the Ministry of Health and the Public Health Lab Service, 24:136, 1965.*

During the course of the Oxford Survey of childhood cancers, data were obtained indicating that children suffering from Down's Syndrome (mongols) are over 30 times as likely to die from this disease as other children. Ninety-eight cases of leukaemia associated with mongolism were compared with 2,848 cases of childhood leukaemia. Each group contained the same proportion of myeloid leukaemias and in both there was a peak incidence during early childhood. The modal age at death was earlier for mongols (second year) than non-mongols (fourth year), and the proportion of males was lower for mongols than non-mongols. In respect of leukaemia incidence and cell types, there were no differences between mongols with old and young mothers, although it is known that advanced maternal age increases the risk of leukaemia in other children. By showing that the same varieties of leukaemia are found in mongols as in other children, the present investigation favors the view that a leucopoietic locus on chromosome 21 can be involved in the genesis of all types of leukaemia. Significance of these findings is discussed in relation to current theories about the origin of leukaemia.

Critique of Left Ventricular Volume Measurement by Indicator Dilution. R. Carleton, A. Bowyer, and J. Graettinger: *Clin. Research, 13:203, 1965.*

The indicator dilution (ID) technique is currently being used to measure left ventricular volume (LVV) in experimental animals and in man. Our studies of LVV had 3 phases. First, LVV estimates were obtained simultaneously in 7 dogs by angiocardiography (angio) and by intraventricular injection of sodium ascorbate with catheter tip polarographic detection, during Fick outputs. Stroke volume (V_E) was the same by angio (13.0 $\pm$ S.E.0.9 ml.) and Fick (13.4 $\pm$ 0.9 ml.). Ejection fraction (V_E/V_{ED}) was significantly higher by angio (0.44 $\pm$ .03 v. 0.29 $\pm$ .01); end-diastolic (V_{ED}) and end-systolic volumes were significantly larger by ID (32 $\pm$ 2 v. 48 $\pm$ 4 ml.; 18 $\pm$ 2 v. 35 $\pm$ 4 ml.). In the second phase, the discrepancy was studied. Localized intraventricular injection and sampling demonstrated smaller "ejection"

fractions at LV apex than outflow in 5 dogs (0.25 v. 0.36; $p < 0.05$) and 7 patients (0.31 v. 0.45; $p < 0.05$); slopes sampled in the aorta were intermediate. Five patients with muscular subaortic stenosis had more gross discrepancies; one with the enhanced mixing of aortic regurgitation had none. Incomplete mixing in LV causes volume overestimates. In the third phase, LV size was altered by blood volume expansion and caval constriction in anesthetized dogs with aortic flowmeters and LV circumference gages. Simultaneously, ID curves were recorded to test directional validity of ID volumes. ID volume changed concordantly with changes in LV size. The ID technique does not measure LVV, but may be a meaningful index of changes in LV size.

Suppression of the Pupillary Light Reflex in Binocular Rivalry and Saccadic Suppression. M. Lorber, B. L. Zuber and L. Stark: *Nature, 208, 558, 1965.*
A direct-recording infrared pupillometer was used to get an objective measure of the human pupillary responses to brief light flashes presented while the subject experienced binocular rivalry. Responses to flashes presented during non-dominance of the stimulated eye were found to be consistently smaller than responses to the same flash presented during dominance of that eye.

The same pupillometer was used to measure the pupillary response to brief flashes presented at various times with respect to the beginning of a saccadic eye movement. It is known that elevation of the visual threshold occurs prior to and during saccadic eye movements. Simultaneous recordings of eye movement and pupillary response revealed that pupillary saccadic suppression occurs concurrently with psychophysical saccadic suppression, but that the two phenomena have different time courses. Maximal pupillary saccadic suppression reduces the pupillary response to 10% of that response elicited by the same flash but presented during steady fixation.

Binocular rivalry and saccadic suppression are two important phenomena involving elevation of visual threshold. The fact that both phenomena have an associated concurrent suppression of the pupillary light reflex yields valuable information applicable to the construction of models of some interactions between oculomotor and visual function.

Significant Factors in the Reimplantation of an Amputated Hand. W. D. Shorey, J. H. Schneewind and H. A. Paul: *Bulletin de La Société Internationale de Chirurgie, No. 1, 1965.*
A successful reimplantation of an upper extremity severed at the wrist is reported. The reestablishment of an adequate venous return is of major significance in the successful achievement of such a procedure. If it is not possible to achieve adequate venous return, multiple relaxing incisions into all closed spaces must be done immediately. Six hours is the maximum time lapse at ambient temperatures permissable prior to surgery for the successful anastomosis of a severed extremity.

Uptake of a New Hydrophobic Fluorescent Dye by Human Platelets. R. M. Lycette, W. F. Danforth, J. L. Koppel and J. H. Olwin: *Proc. Soc. Exptl. Biol. & Med. 117:797-799, 1964.*
A method for uptake of a new hydrophobic fluorescent dye by human blood platelets is described in which cell concentrations are kept constant and those of dye varied widely. Dye uptake is measured in isotonic saline buffered with EDTA at a pH of 3.5, where platelets are near their isoelectric point and dye is maximally affixed to them. Dye uptake did not fit usual patterns of adsorption. At all platelet weights, the amount of added dye bound increased with increasing dye concentration, being nearly proportional to the square of the concentration of remaining dye. Data obtained with platelets from several donors show maxima in per cent of dye taken up and slight differences in these maxima over a wide range of dye concentrations tested. The findings suggest varying levels of hydrophobic substances in or on platelets as well as a means for their assay.

Metabolic Diseases of Bone: Kinetic Studies. R. D. Ray, K. H. Mueller, B. Sankaran, E. D. Mensen and T. B. Schwartz: *The Med. Clinics of North America, 29:1, Jan., 1965.*
1. Studies based on the blood activity and cumulative excretion following intravenous injection of Sr^{85} in ten normal subjects and 25 patients with generalized skeletal disorders are presented and the various methods proposed for analysis of the data reviewed.
2. In normal subjects the mean value for the diffusable component or exchangeable pool

was 20.57 ± 3.74 plasma volumes and the mean rate of clearance of Sr^{85} from this pool by skeletal accretion 2.64 ± 0.74 plasma volumes per 24 hours. In adolescent subjects both values were increased.

3. The values for accretion were decreased in hypoparathyroidism, hypophosphatasia, in one patient with Fanconi's syndrome and in six patients with osteoporosis. The values were increased in vitamin D resistant rickets, Paget's disease and hyperthyroidism. Normal values were obtained in five patients with osteoporosis, one patient with myxedema and one patient with Fanconi's syndrome.

4. Although kinetic studies with tracers cannot be used to replace other means of evaluating skeletal metabolism such as metabolic balance studies, they can serve as a useful adjunct in leading to a better understanding of physiological mechanisms, particularly with regard to rates of mineral deposition and resorption, and they can also be used in evaluating response to treatment. As an example of the latter, several cases of osteoporosis and Paget's disease are cited which were studied before and after treatment.

Indicator Washout as a Function of Ventricular Configuration. A. F. Bowyer, R. A. Carleton, and J. S. Graettinger: *J. Lab. & Clin. Med., 38, Nov. 1965.*

The rapidity of indicator washout (K), defined as the complement of the ratio of concentrations during successive beats, when analyzed for localized regions, should yield information regarding fluid flow patterns within the cardiovascular system. Catheter-tip detection of indicator provides an opportunity to conduct such studies of indicator washout rates in various regions within chambers or vessels. Relative stagnation, characterized by slow indicator washout, has previously been shown near the apex of the normal left ventricle.

Patients with the partially partitioned ventricle of muscular subaortic stenosis were used for the present study. Sodium ascorbate indicator was injected both into the outflow portion and just below the level of the intraventricular pressure gradient. The rate of decline of indicator concentration was measured sequentially in both of these ventricular segments in 6 resting patients and, in 2 patients, during interventions designed to increase the degree of stenosis: isoproterenol and exercise.

At rest, the rapidity of indicator washout was greater from the outflow portion ($K = 0.66 \pm 0.05$) than from the region below the obstruction ($K = 0.27 \pm 0.06$, $p < 0.01$).

During isoproterenol infusion or exercise, the observed increase in the difference between the rate of indicator washout from the apical and from the outflow regions occurred because the K values for the apical region fell from 0.38 at rest to 0.20 with isoproterenol and 0.18 with exercise. This difference between the K values was positively correlated with the magnitude of the peak systolic pressure gradient.

These data support the hypothesis that the rate of indicator washout is a meaningful index of the relative rates of regional blood flow within vessels or cardiac chambers.

Incidence of Malignancy in Giant Pigmented Nevi. P. W. Greeley, J. W. Curtin, and A. G. Middleton: *Plastic and Reconstructive Surgery, 36:1, 26-38, July 1965.*

Giant pigmented nevi create a tragedy to any child or his parents. The etiology has always been obscure but in light of our present knowledge they must be considered congenital malformations.

Most of the documented cases have been single reports. A recent paper stated that there are only 53 cases in the world literature. This is a misleading statement since we have 56 recorded cases from our service alone collected during the past 25 years.

It has long been taught that giant pigmented nevi are purely cosmetic problems and never have malignant potentialities except possibly for the so-called juvenile melanoma. These latter lesions have the identical histologic structure as the malignant melanoma (melanoblastoma) but do not become excited to malignant activity until the onset of puberty. We have learned from personal experience and reported cases of others that this statement is incorrect. Out of 56 cases on our own service, 6 giant pigmented nevi became malignant (over 10 percent). In light of our findings alone, the problem of malignant change is a serious one. Four of our 6 cases died with metastasis. Three of these 4 cases were in children who had been given a diagnosis of juvenile melanoma. These, according to past teaching, could not have had this happen but the metastasis in each were proven at autopsy.

The treatment of giant pigmented nevi is by surgical excision. The resulting defect is then closed either with a large rotation flap or a skin graft. Limitations are created by the

size of the open wound and the skin graft covering that is available. An occasional case may have to be considered inoperable because of the lack of adequate donor sites.

It is emphasized that cvery case of a giant pigmented nevus has a good chance of developing malignant changes. This is especially true with the so-called juvenile melanoma, even before the age of puberty.

Monofunctional and Difunctional Sulfhydryl Inhibitors for Clinical Cancer Chemotherapy. F. E. Knock: *150th American Chem. Soc. Meet., 6-P, 1965.*

The difunctional sulfhydryl inhibitor 3-amino-4-hydroxyarsenosobenzene(I) plus adjuncts has regressed cancers in the majority of patients able to be evaluated objectively (Knock, J. Am. Geriatrics Soc., 13, 313, 1965). To replace arsenicals, iodoacyl and maleimide sulfhydryl inhibitors are being synthesized (Knock, Abs. 149th Meet., Am. Chem. Soc., N-13, 1965) of which monofunctional 2-(N^4-acetylsulfanilamido) ethyl iodoacetate (II) has shown clinical promise for treating patients with cancers sensitive to II on in vitro sensitivity tests. To decrease toxicity and increase solubility, sulfhydryl inhibitors of formula:

$(RNH)_{1-2}$ -X-$(OCOCH_2I)_{1-2}$ .HI with R = H, lower alkyl or CH_2 CH_2OCOCH_2I
and X = alkylene, arylene or aralkylene

have been synthesized. Chemical formulae of the most promising of the group are given in detail.

For clinical cancer chemotherapy with sulfhydryl inhibitors, decrease in stores of normal sulfhydryl compounds (partially protecting tumor from attack by sulfhydryl inhibitors) is desired. Histochemical studies on human cancers regressed clinically by I and II show that H_2O_2 and hyperbaric oxygen (30psi) can be potent sulfhydryl inhibitors. Against human cancers *in vitro*, H_2O_2 and hyperbaric oxygen can potentiate activity of the new sulfhydryl inhibitors, as can
N-(4-biphenylyl)-N-(2-diethylaminoethyl)mandelamide-HCl, clinically useful to combat vasoconstriction and pain produced by sulfhydryl inhibitors.

Ethical Problems of Human Experimentation. F. E. Knock: *J. Am. Geriatrics Soc., 13, 515, 1965.*

Ethical codes for human experimentation are receiving increasing attention. Probably no one doubts that the progress of medicine requires human experimentation. Equally clear, however, is the fact that serious abuses have taken place, and are taking place in this field.

Problems in the field of cancer chemotherapy and heart surgery are discussed in light of the provisions of the Nuremberg Code and the warning in the Statement by Medical Research Council: "It should be clearly understood that the possibility or probability that a particular investigation will be of benefit to humanity or to posterity would afford no defense in the event of legal proceedings." The need of a truly informed consent is noted, for studies on patients, young or old.

Sulfhydryl Inhibitors for Cancer Chemotherapy. F. E. Knock: *J. Indian Medical Prof. (Bombay), 12, 5403-5410, 1965.*

Sulfhydryl inhibitors (agents reacting with, or binding sulfhydryl groups) have been studied for cancer chemotherapy because sulfhydryl-containing residual protein bound to DNA is as indispensable to the structural integrity of chromosomes as is DNA itself and because sulfhydryl inhibitors can preferentially attack cancer cells. Profitable use of sulfhydryl inhibitors, alone and with drugs aimed at nucleic acids, hinges upon the availability of sensitivity tests for matching sulfhydryl inhibitor with its target in the patient's cancer cells. Without direct chemical tests on the target, chemists cannot predict which sulfhydryl inhibitor will react with sulfhydryl groups of even a single protein in solution.

In vitro agar plate assays have predicted results of statistically significant drug assays with animal tumors and results of clinical cancer chemotherapy with both sulfhydryl inhibitors and drugs aimed at nucleic acids. Clinical use of sulfhydryl inhibitors has resulted in objective regression of a variety of human cancers without deleterious effects on bone marrow or wound healing. Clinical use of new sulfhydryl inhibitors free or arsenic (Knock, Abs. 150th Meet., Am. Chem. Soc., 6-P, 1965) has been started for patients whose tumors arc sensitive to the drugs by agar plate assay and for whom the new sulfhydryl inhibitors are the most active of available drugs for the given patient.

Steroid-Antihistaminic Therapy in Experimental Cerebral Edema. R. A. Clasen, P. M. Cooke, S. Pandolfi, G. Carnecki, and G. M. Hass: *Arch. Neurol., 13:584-592, 1965.*
Focal areas of hemorrhagic necrosis were produced in the brains of anesthetized monkeys. The animals were followed for a period of 12 hours, after which they were sacrificed and the cerebral hemispheres analyzed chemically for their electrolyte and water content. In addition, the uptake of iodinated I 131 serum albumin and Evan's blue was determined and the extent of hemorrhage was estimated from changes in the iron content of the tissues. A second group of animals was treated with a combination of prednisolone and chlorpheniramine maleate beginning one hour after injury. These animals were sacrificed at the same time interval and subjected to the same analyses. No evidence that this form of treatment reduced the edema associated with these lesions was obtained.

Brain Reaction to Experimental Injury After Hypothermia. H. L. Rosomoff, R. A. Clasen, R. Hartstock, and J. Bebin: *Arch. Neurol., 13:337-345, 1965.*
The brains of paired dogs were injured by freezing and the course of the reaction to injury was analyzed. One animal of each pair was normothermic at the time of injury, the other was hypothermic at 25 C and then rewarmed one hour after the lesion was made. Comparison, at intervals, of the normothermic and hypothermic groups disclosed reduced exudation and reaction at six hours, and increased inflammation at 24 hours in the hypothermic dogs. One week after injury, a solid wall of granulation surrounded the hypothermic injury, and after two weeks demarcation and collagen formation were striking. At six weeks, the two lesions showed minor differences; at 12 weeks, both were replaced by well-formed mesenchymal scars. It was concluded that demonstrated reductions in mortality by hypothermia resulted from a more rapid transition from the exudative to the reparative stage of the reaction to injury.

Sensitivity Tests for Cancer Chemotherapy. F. E. Knock: *Arch. Surg., 91, 376, 1965.*
Chemical differences in histologically similar tumor are seen in the unpredictable clinical response of patients treated with the same drug for the same type of tumor. Toxic anticancer drugs inactive against the patient's own tumor can injure the patient needlessly by depressing bone marrow, interfering with wound healing, decreasing the patient's resistance to his own tumor and enhancing tumor growth. The possibility of needless injury to the patient from side effects of toxic drugs inactive against the patient's tumor creates a scientific and ethical dilemma for the physician.

In vitro agar plate assays have predicted the known sensitivities of animal tumors to a variety of drugs and results of clinical cancer chemotherapy with sulfhydryl inhibitors and other drugs.

Clinical use of sulfhydryl inhibitors, directed by sensitivity tests, has resulted in objective regression of a variety of human cancers without deleterious effects on bone marrow or wound healing. Use of such sensitivity tests to select drugs for each cancer patient appears to conform to the spirit and exact provisions of the Nuremberg Code, Declaration of Helsinki and the Statement by Medical Research Council.

Management and Complications of Severe Pulmonary Burn. W. L. Donellan, S. M. Poticha, and P. H. Holinger: *JAMA, 194:12, Dec., 1965.*
A 5-year-old boy burned in a tenement fire sustained severe broncho-pulmonary burns without apparent initial signs of heat injury to the oral cavity or pharynx. However, increasing respiratory obstruction in the second 12 hours necessitated a tracheostomy because of excessive mucus and edema of the tracheobronchial tree. Survival was aided by antibiotic therapy and by positive-pressure ventilation of aerosolized bronchodilators as well as by steroids added to the tracheostomy nebulizing system of the respirator. The latter apparently reduced the marked bronchial obstruction which developed during the first few days. Early fluid requirements were higher than anticipated, perhaps because of the severity of the pulmonary burn. The late development of bronchial stenosis and bronchiectasis is apparently the result of damage to the submucosa and musculature of the bronchi caused by the heat injury incurred by the inhalation of hot gasses and the secondary infection. The stenosis and bronchiectasis were demonstrated within the first year after discharge of the child from the hospital.

Parasympathetic Influence on the Atrial Myocardium and Myocardium and Atrioventricular Node of Man. R. A. Carleton, J. S. Graettinger, and A. F. Bowyer: *Jour. of Lab. & Clin. Med., 66, 413, 1965.*

The hearts of 5 subjects of varying degrees of physical conditioning, ranging from sedentary to physically fit, were paced by means of a catheter-pacemaker in the right atrium in order to bypass the effects of the sinus node. With heart rate controlled, the magnitude of autonomic effect on the atrial myocardium and on the atrioventricular (A-V) node could be investigated. Evidence that parasympathetic tone influenced the electrical response of the atrial myocardium was found in the most fit athlete. The spectrum of sinus nodal rates was paralleled by the observed spectrum of A-V nodal conduction. Individuals with high vagal tone have ventricular rates which are limited not only by sinus activity but also by A-V nodal conduction.

A Cause of Low Back Pain. F. M. Howard: *Chicago Medicine, 67, 7410743, Sept., 1964.*

The cause of most back pain is due to aging of the intervertebral disc and subsequent fragmentation. These discs have little or no blood supply after the age of twenty years. They are presumably nourished by the exchange of metabolites. The discs apparently have no nerve supply except to the anterior and posterior longitudinal ligaments and possibly the superficial layers of the annulus. Therefore, their capacity for regeneration and repair is very limited. Yet, these discs are subjected to severe strain and stress. It has been calculated that lifting a 100 pound load places a stress of 1500 pounds on the lumbosacral disc space.

How does an insensitive disc become sensitive and cause low back pain? The following represents the pathomechanics: 1—Disc ages and fragments, 2—Tears and cracks occur in annulus, 3—Granulation tissue invades the cracks and brings in a nerve supply, 4—Low grade inflammation follows, 5—Painful disc.

Once the ground work is established for an abnormal and sensitive intervertebral disc, there are *three sources of pain in this type of back*: 1—Mechanical, unstable lumbar spine, 2—Ligament strain and muscle spasm, 3—Incarceration or irritation of the nerve root.

The most frequent cause of low back pain is a degenerative lumbar disc. This can cause pain in three ways—a mechanically unstable lumbar spine, muscle spasm with ligament strain, or irritation of a spinal nerve. Treatment is essentially directed at supporting the mechanically inept lumbar spine.

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SYMPOSIUM ON SHOCK

Septic Shock

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SEPTIC SHOCK:
Laboratory Developments in Their Relation to Therapy

James H. Freel, M.D.[1]
Harold A. Paul, M.D.[2]

INTRODUCTION

In 1899 Brill and Libman[1] described a patient who developed a positive blood culture for Pseudomonas Aeruginosa. When the patient died subsequently, autopsy revealed an abscess. The source of this abscess was not clear. A review of the case report indicates that the patient had chills, fever, tachycardia, and tachypnea progressed to a weakened state. Hence, although the term "shock" does not appear in the report it is likely that this patient indeed died in septic shock.

In 1951 Waisbren[2] first described a clinical syndrome which was characterized by the appearance of Gram-negative bacteremia in patients in shock. Increased activity by many investigators followed Waisbren's report. Several laboratory models were developed. As in the case of hemorrhagic shock the experimental model differs in significant ways from the clinical problem which it is designed to elucidate. These differences may be understood by considering some definitions.

Shock: While a precise definition of shock defies approach, it is practical to consider shock as a syndrome of inadequate effective tissue perfusion of the vital organs. This inadequate perfusion produces a wide range of effects upon the whole organism.

Gram-negative septicemic shock: This is a clinical syndrome in which Gram-negative bacilli are known to be present in the circulating blood.

Endotoxin: Endotoxin is a heat stable high molecular weight, phospholipid-polysaccharide-protein complex.[4,5] Its antigenic specificity is determined by the carbohydrate portion of the molecule, while is toxicity is derived from the lipid fraction. Such toxicity is thought to be present only when the lipid is conjugated with polysaccharide or protein.[5,6] Various extraction methods have been used to prepare endotoxin. With each extraction method the antigenicity as well as the toxicity varies. For this reason, one may expect to see non-uniformity in experimental models.

Most workers have studied endotoxin shock in dogs. Some have used mice, rabbits, rats, cats and monkeys. Following Spink[7] and Waisbren[2,8] the most commonly used dose range is 1 to 4 milligrams of endotoxin per kilogram. This is usually the endotoxin derived from Escherichia coli.

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The immediate sequel to this dose of E. coli endotoxin in the dog is the development of systemic hypotension and portal hypertension which begins within five minutes. There is also an associated severe metabolic acidosis. Intravascular coagulation defects have also been noted. Within five to thirty minutes there is a return towards normal in the systemic hypotension, the portal hypertension, and metabolic acidosis.

The dog proceeds to die in shock usually within 10 to 18 hours. At this time he will have developed a slowly progressive hypotension and a progressive relentless severe metabolic acidosis.

Among autopsy findings in dogs that succumb to endotoxin shock, one may find areas of severe hemorrhage in the mucosa of the small intestine, and hepatic and renal engorgement. These autopsy findings resemble those of the dog which dies in hemorrhagic shock. It is a well-known fact that in humans dying from septic shock, hemorrhagic small bowel mucosa is not found. Among many possible reasons for these differences, two can be cited. First, among animals which develop shock each reacts in a way that is peculiar to his own species. Second, endotoxin shock is produced by a single massive injection of endotoxin with maximal metabolic reactions occurring rather quickly. Septic shock, on the other hand, may develop at varying rates of speed and there is no way at present in which we can assess the kind of toxin or its rate of "injection."

A shock model which is similar in some respects to the animal in endotoxin shock has been developed by Nickerson.[9] By giving infusions of epinephrine or norepinephrine during a four-hour period in a dosage of 1 to 4 micrograms per kilogram per minute, he has produced shock leading to death in animals. Hemorrhagic mucosa develops in the small intestine in both groups of animals. Nickerson believes that over-activity of the autonomic (sympathetic) nervous system is a leading feature in shock. Such autonomic activity produces vasoconstriction in the splanchric bed. This type of shock can be reversed by administering an alpha-receptor blocking agent.

Lillehei[10] has reversed endotoxin shock in dogs by giving dibenzyline (1 mg/kilogram) along with plasma expanders. In this study survival rates ranging from 60% to 80% have been produced.

Hardaway[11] has studied intravascular coagulation defects in endotoxin shock. It is believed by MacKay[12] that such intravascular coagulation occurs in many forms of stress and not only in shock. MacKay and Shapiro[16] have produced generalized Shwartzman reaction in rabbits by in vivo injection of endotoxin. The first injection rapidly causes a hyperfibrinogenemia. The second injection lowers the fibrinogen rapidly but high levels return within 20 hours. The blood is hypercoagulable four hours after each injection. Before the Shwartzman reaction there are elevated fibrinogen levels, leukocytosis and thrombocytopenia. Gans and Krivits[17] have shown a variable fall in fibrinogen and a decrease in plasminogen following endotoxin administration in dogs. They found that heparin pretreatment prevented death from 0.1 milligrams of endotoxin but not from larger doses. Therefore, they suggest that endotoxin precipitates intravascular clotting and hemorrhage results from rapid lysis of these clots. In irreversible hemorrhagic shock, Hardaway believes that disseminated intravascular coagulation also occurs.[13] He has shown that ganglionic blocking agents protect in this form of shock.

In this general field, investigation in our laboratories was aimed at outlining the course of metabolic acidosis in endotoxin shock in dogs. Ph, pCO_2 standard bicarbonate and base excess or base deficit were determined by use of the Astrup methods. In order to standardize dosage and response an LD-50 for E. coli endotoxin 0127:B8 (control number 151782) was determined. Graded doses were given to 150 dogs to develop a dose —response curve. The dose required to produce 50% mortality was 12.9 micrograms per kilogram, 95% confidence limits of LD-50 (R0.001365 milligrams

lower limit and 0.1219 milligrams upper limit). This is an infinitesimal dose compared to that usually reported, 1 to 4 milligrams per kilogram.

Autopsy findings in the dogs which died revealed congestion in the small intestine without hemorrhagic mucosa. Congestion in the kidneys was also noted.

In the period before death, metabolic acidosis developed but this was slower in onset and less severe, early in the course. However, severe metabolic acidosis developed during the 12 to 24 hour period.[13]

OUTLINE FOR TREATMENT

The evidence reviewed above indicates that controversy still exists at many points regarding etiology and treatment for septic shock. A consensus of current ideas on treatment would suggest the following outline as a therapeutic approach:

A. Obtain cultures of infected sites and several blood cultures.
B. Introduce central venous pressure monitoring system.
C. Introduce indwelling catheter for hourly urine output and specific gravity.
D. Consider venous cutdown if there is any difficulty in maintaining at least two infusion systems.
E. Give antibiotics. At present chloramphenicol, penicillin and streptomycin are most commonly used. It is our practice to give these antibiotics from the first hour in very high doses intravenously.
F. Vasodilators, in our opinion, should be used in preference to vasoconstrictors. At the present time we use no vasoconstrictors but we admit that this exclusion is by no means settled. Drugs which are commonly used for a 'vasodilator' effect are:
   1. Chlorpromazine 0.2 mg/kg—50% of calculated dose in 30 minutes and subsequent dosage as needed.
   2. Hydrocortisone 50 mg/kg. This should be given in the first 1 to 4 hours and repeated as needed in the first 21 to 24 hours.
G. Plasma expanders, plasma or blood must be given vigorously along with vasodilators. By the use of vasodilators and plasma expanders we hope to achieve adequate urinary output and adequate tissue perfusion as shown by speed of the blanching reaction and the disappearance of clammy skin.
H. A diligent search for an obscure source of infection is frequently a fundamental point in treatment.
I. Certain laboratory data would appear to be of special value. We have followed the pH, pCO_2 base excess and studies by use of the Astrup method.[15] While we agree that no conclusive laboratory data yet exist to prove that maintenance of good acid-base balance is of critical significance in septic shock, it is our practice to treat these deficits with sodium bicarbonate or with THAM.
J. The usual parameters such as temperature, pulse, respirations and blood pressure, hematocrit, hemoglobin, and WBC are all of great importance. □

SUMMARY

Septic shock associated with Gram-negative septicemia is a severe disease which requires vigorous treatment. Much information has been gained from endotoxin shock as a laboratory model, but animal models differ from septic shock patients in ways that are easily recognized. It is possible that a LD-50 dose of endotoxin can produce a laboratory model which more closely resembles Gram-negative septicemic shock. An outline of our present method of treatment is included.

□

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HEMODYNAMIC CHANGES DETERMINING THE TREATMENT OF SHOCK

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INTRODUCTION

The clinical syndrome of shock results from complex interrelated hemodynamic, metabolic and hematologic changes produced by a variety of stresses. Although the precise changes vary with the initiating trauma, the responses tend to follow a common pattern.

Of necessity much of our knowledge of these changes is derived from animal studies although modern monitoring techniques, which provide much objective data with minimal disturbance to the patient, are rapidly extending our understanding of the pathogenesis of shock in man. It is rightly cautioned that species differences do not allow uncritical transfer of conclusions from animal studies to man,[1,2] but it also seems that many of the differences in the observed changes are more apparent than real.[3]

The nature of these changes also varies in different regions of the circulation. In general, the initial compensatory response involves a sharp reduction in flow to immediately non-vital areas to maintain perfusion of the vital organs. But with passing time, harmful sequelae result from prolonged ischemia of the former areas which, if uncorrected, finally determine the death of the organism.

The first aim of treatment is to correct the cause of the shock. This may allow restoration of a normal physiological state but in many patients with severe or protracted shock spontaneous return to normal will not occur. In this situation judicious ancillary treatment based on understanding of the hemodynamic derangement may be of benefit.

PATHOGENESIS

Shock may be considered as a syndrome resulting from critical impairment of effective circulating blood volume. This may be caused by a disparity between the blood volume and the vascular bed or by inadequate cardiac pumping. The ultimate effect is impairment of tissue perfusion, oxygenation and aerobic metabolism, necessitating development of anaerobic metabolic pathways.

Reduction of Perfusion Pressure

A decreased blood volume will result in impairment of flow through all regions simply by virtue of a reduced perfusion pressure gradient. Uncorrected, a vicious cycle would be set up of impaired venous return and cardiac output with increasing hypotension. (Fig. 1)

Sympathetic Vasoconstriction

However, hypotension also results in reflex sympathetic vasoconstrictor discharge[4] and this produces several effects.

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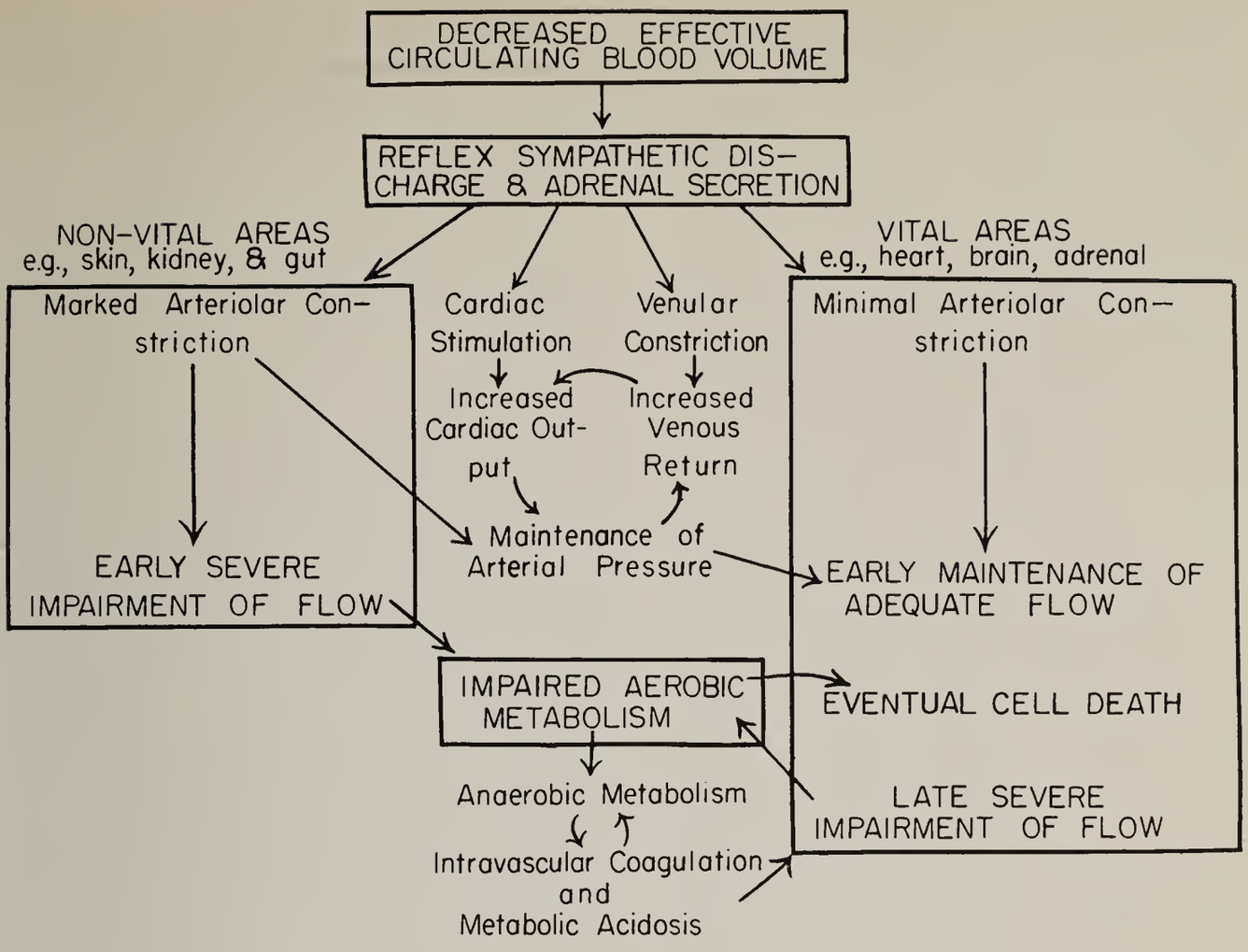
DECREASED EFFECTIVE CIRCULATING BLOOD VOLUME
REFLEX SYMPATHETIC DIS-CHARGE & ADRENAL SECRETION
NON-VITAL AREAS e.g., skin, kidney, & gut
VITAL AREAS e.g., heart, brain, adrenal
Marked Arteriolar Con-striction
Cardiac Stimulation
Venular Constriction
Minimal Arteriolar Con-striction
Increased Cardiac Out-put
Increased Venous Return
Maintenance of Arterial Pressure
EARLY SEVERE IMPAIRMENT OF FLOW
EARLY MAINTENANCE OF ADEQUATE FLOW
IMPAIRED AEROBIC METABOLISM
EVENTUAL CELL DEATH
Anaerobic Metabolism
LATE SEVERE IMPAIRMENT OF FLOW
Intravascular Coagulation and Metabolic Acidosis

Fig. 1.—Schematic representation of the hemodynamic and metabolic responses to shock.

Firstly, rapid, marked arteriolar constriction occurs in certain tissues as a result of stimulation of the so-called *alpha* receptors in the vascular smooth muscle, transmission being mediated by nor-epinephrine liberated from the nerve endings.[5] (Fig. 2) Under normal conditions the influence of these constrictor mechanisms is most marked in the skin and renal circulations and less marked in muscle and in the splanchnic viscera while sympathetic vasoconstriction is not apparent in the coronary, cerebral and adrenal circulations.[6] (Fig. 1)

The increase in precapillary resistance results in an initial decrease in capillary hydrostatic pressure with passage of extravascular fluid into the circulation and hemodilution. In the late stages of shock, the peripheral vessels gradually become unresponsive to continued vasoconstrictor discharge and progressively dilate[7] although responsiveness partly returns after retransfusion.[8] This arteriolar dilatation results in a secondary increase in capillary pressure and slight loss of intravascular fluid,[4,9] but there is no evidence of significant terminal loss of intravascular fluid leading to hemoconcentration either from capillary congestion or increased capillary permeability in man.[3]

Secondly, vasoconstriction also affects arteriovenous shunts. That part of the blood flow which passes through capillaries can be indirectly measured by the degree of extraction by the tissues of certain isotopes injected intraarterially and the difference between this and the total flow represents flow through shunts. A proportionately greater decrease in isotope extraction compared with total flow has been found in the dog's gut in both hemorrhagic[10] and endotoxin[11] shock and this has been interpreted as indicating relatively greater constriction of precapillary vessels than of shunts resulting

in diversion of flow away from capillaries to non-nutritive pathways. These shunts are widespread, having been demonstrated in the gut,[12] kidney,[13] liver,[14] muscle,[15] and skin.[16] Their significance in shock in man is virtually unknown.

Thirdly, *alpha* adrenergic stimulation also results in generalized venular constriction causing mobilization of blood to increase venous return. (Fig. 1) Folkow[17] has indicated that as little as a 2% shortening of venular smooth muscle could theoretically double diastolic filling. In the late stages of shock gradual venular dilatation also occurs but the commonly accepted concept that peripheral pooling, particularly in the splanchnic viscera, contributes to the development of the terminal changes is disputed. For example, the weight of the gut of the dog does not increase in the terminal stages, even after retransfusion, in hemorrhagic shock.[18] Kuida et al.[19] showed no increase of weight of the gut in a variety of animals following endotoxin shock although McLean et al.[20] found a moderate increase in gut weight and a marked increase in weight of the liver in the dog.

Fourthly, sympathetic stimulation also results in an increased force and rate of cardiac contraction, this being mediated through the so-called *beta* receptors.[5] (Fig. 2)

The increased peripheral sympathetic activity is sufficient to allow overflow of nor-epinephrine into the general circulation, and the blood levels rapidly increase by some three to four times in the animal;[21,22] contribution from the adrenal gland is minimal as prior adrenalectomy does not prevent the rise.[22,23] In the later stages of shock this results in marked depletion of nor-epinephrine stores in the nerve endings, both generally[24] and particularly in the heart,[25] and it is possible that this is a factor in terminal vasodilatation and impaired cardiac function.[26]

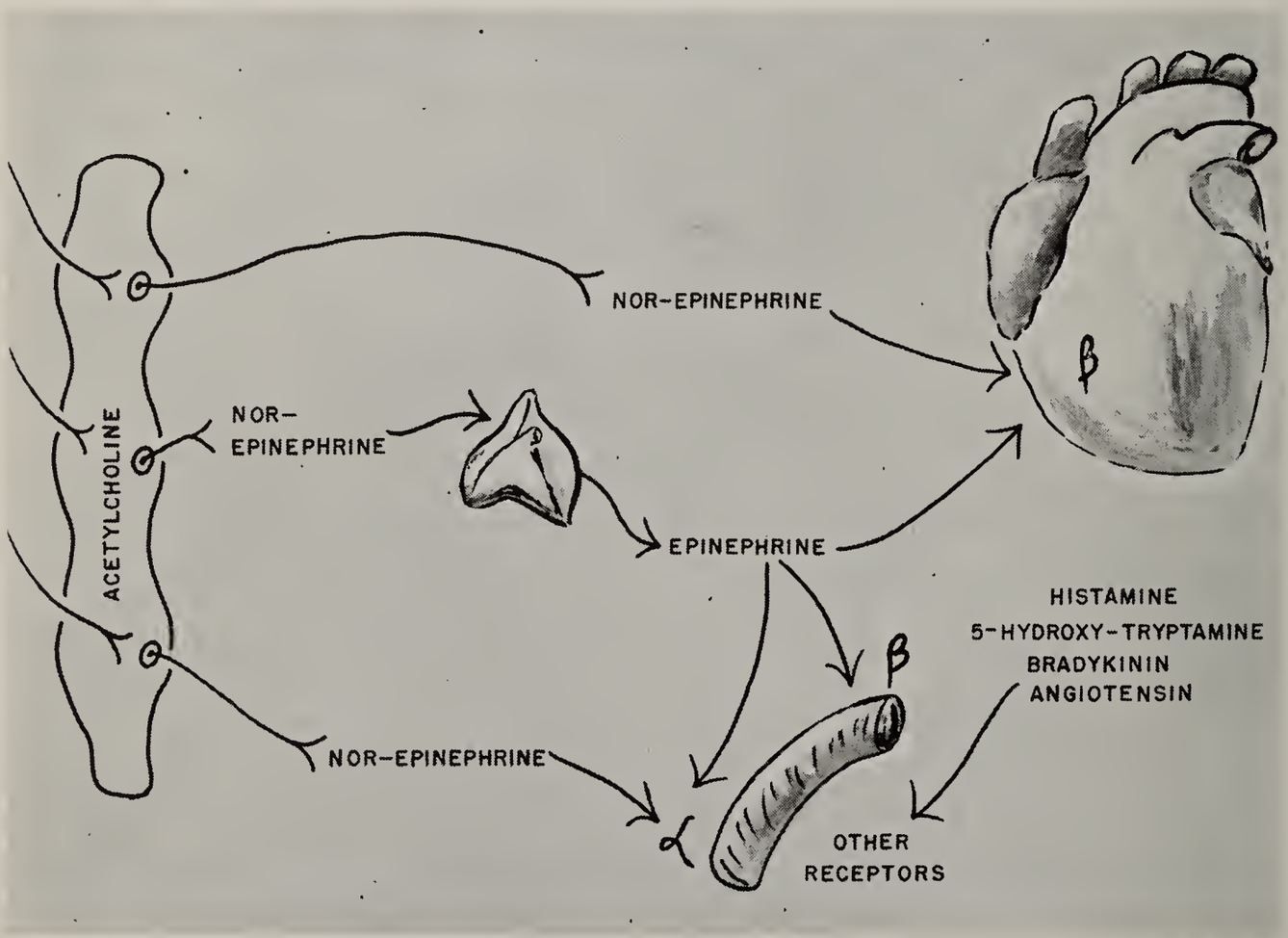

Fig. 2.—Schematic representation of the pathways responsible for the sympathetic nervous and adrenal response to shock. It shows the effect of the catecholamines and other endogenous vasoactive compounds on the heart and peripheral vessels, mediated through γ, β and other receptors.

Adrenal Catecholamine Secretion

Sympathetic discharge also results in increased adrenal catecholamine secretion, predominately of epinephrine, in both hemorrhagic[21,23,27] and endotoxin[22,27] shock. (Fig. 2) In the dog, blood levels of epinephrine increase by up to one hundred times in the general circulation[28] and by over one thousand times in the adrenal vein.[22] These increased levels are apparent both initially and again in the terminal phases indicating the absence of terminal adrenal failure.[27] Epinephrine results in stimulation of both the *alpha* receptors at the periphery and *beta* receptors in the heart and this produces similar regional affects to nor-epinephrine and sympathetic discharge. In addition, it stimulates the non-innervated *beta* adrenergic receptors at the periphery; these are essentially confined to muscle and the gut and their stimulation normally results in vasocilatation[5] but this effect is completely masked in shock.

The response to nor-epinephrine and epinephrine is markedly depressed in the late stages of shock possibly as a result of metabolic acidosis[29,30] and this may provide a further mechanism for terminal vasomotor and cardiac collapse. Little is known of changes in catecholamine levels with shock in humans.

Autoregulation

In those areas which are not subject to sympathetic control, a decrease in peripheral resistance occurs during shock possibly as a direct myogenic response to decreased intraluminal pressure[31] or from a tendency to local accumulation of metabolites.[32] This further facilitates perfusion of the vital centers. Autoregulation is most marked in the cerebral circulation although vasodilatation here primarily results from increased levels of blood CO_2.

Hematologic Changes

Several authors[34,35,36] have postulated that following prolonged severe vasoconstriction hematologic changes result from stagnation of flow, accumulation of toxic products in the blood and changes in the plasma proteins. Gelin[34] considers that red cells agglutinate at low flow rates into a sludge probably as a result of incorporation of the cells in a gel-like matrix of plasma proteins, particularly fibrinogen and globulin.[37,38] Hardaway[36] goes even further and gives evidence of actual intravascular coagulation with incorporation of platelets and red cells in a fibrin clot. Peripheral sequestration of these components may result in anemia[39] and in depletion of clotting factors and platelets with an increased bleeding tendency.[36] The resultant rise in viscosity would further increase peripheral resistance ultimately resulting in cessation of capillary flow, and total flow through the organism would be increasingly maintained through opening of arteriovenous shunts; ultimately irreversible necrosis would result in the parenchymal organs.[40]

These concepts are not yet universally accepted, many feeling that the observed changes are artefacts[3] or that at best they are a result rather than a cause of the terminal deterioration.

Changes in Peripheral Resistance

As a result of the variable vasoconstriction and dilatation in different regions, changes of the total peripheral resistance are usually not particularly striking, in either the animal or man. Following hemorrhage in the animal mean increases of up to 90% have been reported by some[41,42] but little change has been demonstrated by others.[43] During endotoxin shock the total peripheral resistance initially rises then falls.[44] In man, the total peripheral resistance is most commonly increased in both cardiac and hypovolemic shock and decreased in septic shock[45] but individual patients show marked variability.[46]

Of necessity, most studies of regional changes have been performed in animals. Following severe hemorrhage in the dog the greatest increase in peripheral resistance, of up to 160%, occurs in the extremities, particularly in the skin.[47,48] Almost comparable increases occur in the renal circulation,[49,50] particularly in

the cortex which normally carries most of the renal flow, and the pulmonary resistance also rises.[51] Contrary to the usual teaching, changes in the splanchnic circulation are not striking; many authors find that total splanchnic resistance changes little[41,48,52,53] or if at all, late in shock[54] but others find a variable rise.[50,55] The increase is considerably more apparent in the portal than in the hepatic arterial circulation.[48,53,55,56] In contrast, the vascular resistance falls during severe hemorrhage in the circulations through the brain (by some 40%)[57] and myocardium (by some 5% to 45%).[47,49,51] Similar changes occur in endotoxin shock although the initial increased resistance in the peripheral, renal, and pulmonary circulations rapidly returns to control levels.[44]

In man, Lauson[58] has shown marked renal vasoconstriction during shock and in a remarkable study, Stone et al.[59] have measured a 34% decrease in cerebral resistance during experimental hemorrhagic shock in humans.

Changes in Blood Flow

The cardiac output is virtually always reduced in each type of shock and this is associated with a decreased velocity of flow and increased circulation time.[46]

Whereas, peripheral, renal, and splanchnic flows fall severely, there is a less marked decrease in the coronary flow (by some 10% to 30%)[49,51] in the animal and in the cerebral flow (by some 26%)[59] in man; that is, proportionately more of the cardiac output is being directed to these areas.

Changes in Oxygen Consumption—Aerobic Metabolism

In spite of an increased extraction of oxygen from blood, impaired tissue perfusion in severe shock rapidly results in tissue anoxia. The total oxygen consumption in the animal falls during hemorrhagic shock[60] and the extent of the fall bears a striking relation to the mortality.[61] Decreased tissue oxygenation necessitates development of far less efficient anaerobic pathways and if anoxia is sufficiently severe, irreversible cellular changes will eventually result. The rate of development of these changes in different regions depends on the degree of impairment of flow and the sensitivity of the tissue to anoxia.

Cerebral oxygen consumption is actually increased during hemorrhagic shock in man.[59] Myocardial oxygenation in the animal has been found to be maintained[62] although Edwards et al.[63] showed an appreciable fall. Guyton and Crowel[61] believed that myocardial failure initiates "irreversibility" but, although myocardial contractility falls terminally in shock,[64] Simeone[65] has shown that it can recover to normal levels after retransfusion even though the animal will ultimately die. Clearly, decrease in cerebral or coronary flow normally insufficient to compromise oxygenation may do so in a patient with preexisting arterial disease.

The area most sensitive to anoxia is apparently the splanchnic viscera. Marked decrease in oxygen consumption, oxidative phosphorylation and nucleotide synthesis rapidly develop in both the gut and liver; in those dogs that die these processes fail to return to normal in the gut following transfusion although they temporarily do so in the liver.[66,67] That the splanchnic viscera play an important role in the genesis of the terminal changes is indicated by the increased survival rates resulting from measures to protect the gut[27] and liver.[3]

Effects of Anaerobic Metabolism

The metabolic acidosis resulting from accumulation of lactate and pyruvate is fully discussed elsewhere in this issue.[68] Less is known about the influence of other metabolic disturbances on the hemodynamic changes. Oxidative phosphorylation occurs in mitochondria and functional changes of swelling and eventual fragmentation are seen in the mitochondria, particularly in the liver[69] and heart,[70] although it appears that their function is maintained. ATP and other high energy phosphate compounds are lost from the mitochondria although this is not irreversible, rapid replenishment occurring following retransfusion.[71] Both

hemorrhagic and endotoxin shock cause disruption of intracellular lysozomes allowing liberation of proteolytic and other enzymes.[72] Cellular damage probably allows liberation of many other compounds. Thus, serum potassium levels rise;[3] liberation of histamine may result in hepatic venous and pulmonary constriction;[44] bradykinin and other polypeptides may produce the terminal vasodilatation, particularly in septic shock and hemorrhagic pancreatitis;[73] 5-hydroxy-tryptamine levels are markedly elevated and this may initiate platelet aggregation with the formation of microemboli.[74] No evidence has been found to implicate ferritin (VDM) as an important agent,[75] while evidence regarding the significance of endotoxin absorbed from the gut in all types of shock is disputed.[3] Little is known of the importance of these substances in man.

TREATMENT

From these considerations it is possible to comment on the rationale of a host of agents used in the treatment of shock. Naturally, the primary aim of treatment is to correct the underlying cause, be it by infusion of appropriate fluid to correct hypovolemia, by augmentation of the failing heart or by antibiotic treatment for septicemia. But if this is insufficient it may be necessary to concurrently institute other measures to improve cellular oxygenation.

Vasopressor Drugs

In spite of many papers condemning their use, it is probably true that these agents are used and abused in shocked patients more than any other single form of drug treatment. The rationale for their use is to augment the physiological compensatory mechanisms, either by cardiac stimulation or by production of vasoconstriction of the visceral and peripheral circulations or both, so as to maintain perfusion of the vital centers. This would be reasonable only in the early stages of shock and not when ischemia of the viscera and other regions is producing lethal toxic changes. Moreover, it is reasonable only if coronary and cerebral ischemia is threatening life which, in the early states, is not usual.

In the experimental animal, infusion of nor-epinephrine or epinephrine produces an increase of the cardiac output.[57,76,77] Cerebral flow and oxygen consumption are increased in spite of an increased vascular resistance,[57,78,79] while in the myocardium, flow is increased some three to four times with a considerable rise in oxygen consumption as a result of fall in resistance.[47,57,77,78] The changes in the splanchnic viscera and kidney are variable; with small doses flows increase[80] but amounts sufficient to establish a normal arterial pressure cause further marked reduction of perfusion;[52,57,80] the resistance of the peripheral vessels is markedly increased.[47,77] The development of metabolic acidosis is accelerated[81] and this and other mechanisms rapidly produce further reduction in the responsiveness to the catecholamines.[6,29,30] Death of the animal is, if anything, more rapid.[27,57]

Many other vasopressor agents have been developed, the actions of some being shown in Fig. 3. There is some evidence, again mainly in animals, that metaraminal (Aramine) is less harmful than nor-epinephrine. Doses sufficient to cause a comparable rise in pressure produce an increase in splanchnic and renal flow[82] and slowing of the development of metabolic acidosis.[81]

It thus seems reasonable to administer Aramine in a few selected circumstances. Firstly, in cardiogenic shock or where a marked cardiac element accompanies hypovolemic shock, cardiac stimulation by vasopressor agents might allow improved peripheral perfusion although care must be taken to detect impending arrhythmias; benefit will be achieved only with early treatment.[83] Secondly, in septic shock where cardiac impairment

and peripheral pooling may be important elements, cardiac stimulation with arteriolar and venular constriction may allow considerable improvement in venous return, cardiac output and peripheral perfusion while awaiting effect from antibiotics; however, Weil et al.[84] did not gain encouragement from the results of treatment in clinical cases. Thirdly, in exceptional cases of hypovolemic shock early treatment even with considerably larger doses, may be temporarily required to improve cerebral or coronary perfusion if shock is very severe or if there is previous known coronary or cerebral atheroma; patients in the late stages of hypovolemic shock who are unresponsive to transfusion will also be unresponsive to vasopressors.

Except in emergency circumstances the dose of a vasopressor drug should be small and given at a rate which will not elevate the arterial pressure to more than 20 to 30 milimeters of mercury below normal. One hundred to two hundred milligrams of Aramine diluted in five hundred ml. of fluid, given over about one hour, should be adequate.

Angiotensin (Hypertensin) mainly acts to constrict arterioles, particularly in the gut, and has little effect on venules or on cardiac contraction; it is thus theoretically unsuitable for the treatment of shock.

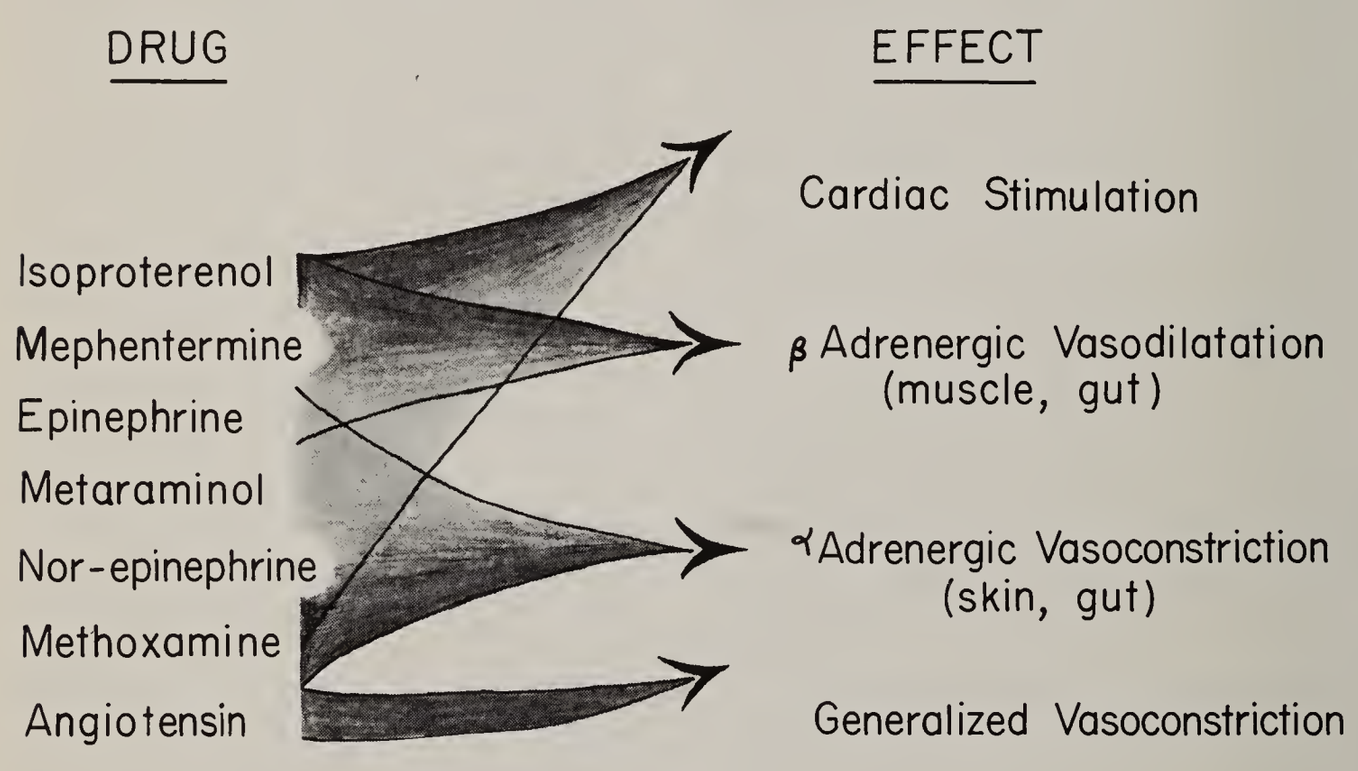

Fig. 3.—Schematic representation of the hemodynamic effects of several vasopressor agents which might be used in the treatment of shock.

Vasodilator Drugs

Appreciation of the harmful results of prolonged ischemia, particularly of the splanchnic viscera, as a possible origin of the changes causing death has led to measures to improve perfusion in these areas. Of course, such measures are rational only if they do not compromise flow to the heart and brain by producing hypotension.

Thus, Fine[3] has shown that celiac denervation increases survival, improves cardiac output and reduces metabolic acidosis in the animal and he has used celiac xylocaine blocks in clinical patients.

It is more common to employ systemic administration of vasodilator drugs, the site of action of some of these being indicated in Fig. 4. The alpha adrenergic blocking agents block both sympathetic

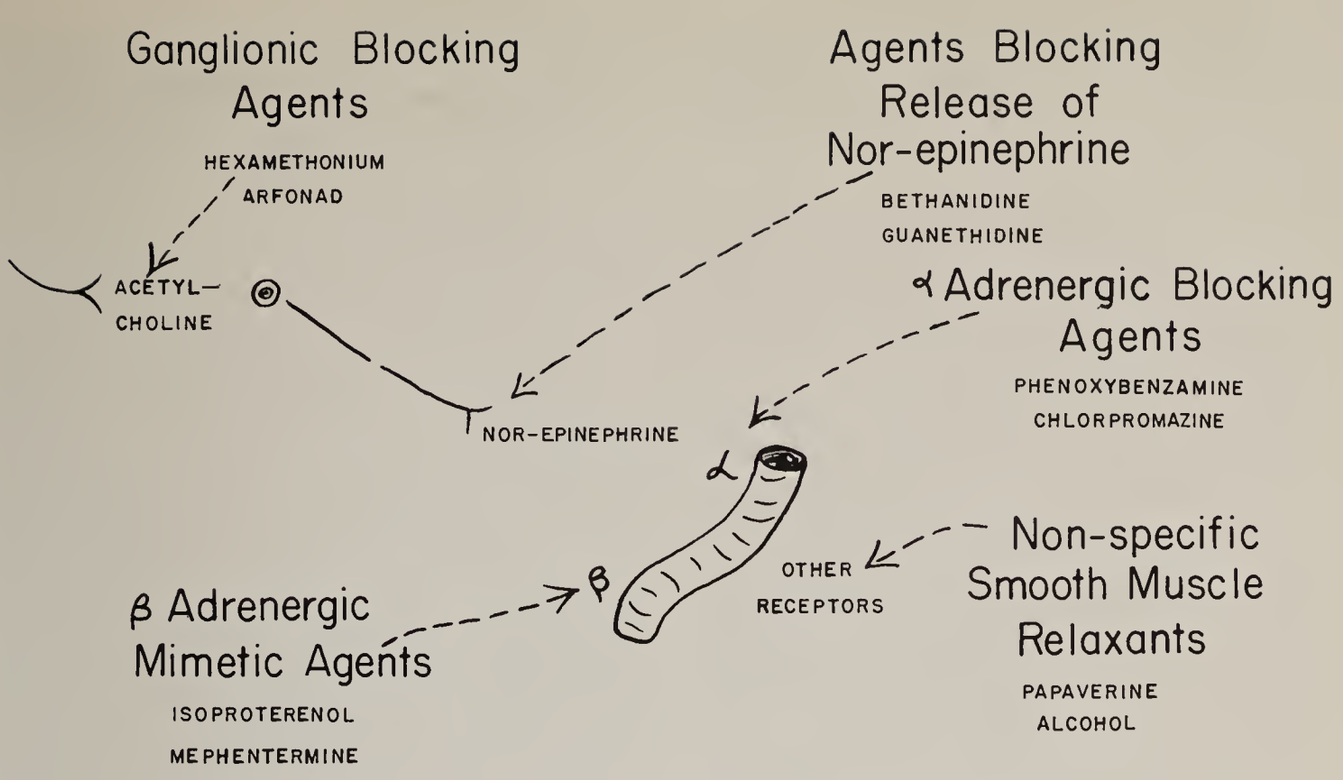

Fig. 4.—Schematic representation of the site of action of several vasodilator agents which might be used in the treatment of shock.

vasoconstrictor discharge and the circulating catecholamines and are thus more appropriate than the ganglion blocking agents or substances preventing release of nor-epinephrine from the nerve endings, which block only the former. These substances frequently have multiple actions; for example, phenoxybenzamine (Dibenzylene) also blocks histamine, 5-hydroxy-tryptamine and acetylcholine, some of which may be important in septic shock.

In animal studies, increased survival has been demonstrated in hemorrhagic shock following pretreatment with an alpha blocking agent[84,86] and even with treatment commenced up to three hours after the onset of shock,[87,88] while increased survival has also been demonstrated with such treatment in endotoxin shock;[27,89] it must be admitted that other studies fail to show increased survival with treatment started after the onset of shock.[86,90]

The actual hemodynamic changes seen in the animal following infusion of a vasodilator drug depend on the conditions of the experiment; for example, if transfusion is not allowed, opening up of the vascular space may reduce venous return, cardiac output, and tissue perfusion. Under suitable condition, it can be shown that the drug can increase cardiac output, mesenteric and renal flows, decrease portal and pulmonary resistance,[27,91,92] and reduce metabolic acidosis[89] and intravascular coagulation.[36] In clinical patients, Wilson[93] has shown improvement of cardiac output with decrease in total resistance and central venous pressure, and increase of urine flow.

Continued vasoconstriction may allow maintenance of an acceptable arterial pressure in the face of significant persisting hypovolemia. Reversal of the vasoconstriction by a vasodilator drug may thus allow adequate restoration of the blood volume without cardiac overloading. In patients who are not showing adequate improvement with transfusion, Dibenzylene may be given by slow intravenous drip in a dose of 1 mg/kg over one to two hours, only provided that the transfusion is running and that frequent measurements can be made of arterial

and central venous pressures to adjust the relative rates of blood and drug infusion.

Hydrocortisone

In spite of the fact that adrenal steroid production is elevated in shock in both animals[94] and humans,[95] increased survival has been reported in the dog and man following treatment with large doses of hydrocortisone[27,85,88] or aldosterone[96] both in hemorrhagic and endotoxin shock. The mechanism of benefit is not clear but it is known that high doses produce vasodilatation[85] and also stabilize the intracellular lysozomes preventing their disruption.[72] It seems that a large intravenous dose of 1 gm. of hydrocortisone repeated in one to two hours, or 50 mg. dexamethasone or 200 mg. methylprednisolone repeated in four to six hours, will do no harm and may do good in severe refractory cases.

Combined Drug Treatment

It has been recommended that the beneficial cardiac stimulant effects of nor-epinephrine may be utilized with blockade of the possibly harmful peripheral vasoconstrictor effects by concurrent administration of phenoxybenzamine. While rational, the efficacy of this combination in man is unknown. Other catecholamines, the beta adrenergic mimetic agents such as isoproterenol (Isuprel) and mephenermine (Wyamine) achieve this combination of cardiac stimulation and peripheral vasodilatation, particularly in the gut and muscle, and are theoretically ideal agents. Increased splanchnic blood flow but with insignificant change of oxygen consumption has been demonstrated with Isuprel in the animal[97] and striking benefit from this drug has been demonstrated in the shocked animal and man.[98,99] Improvement of results has also been demonstrated in animals with a combination of hydrocortisone and phenoxybenzamine,[88] phenoxybenzamine and isoproterenol,[89] and aldosterone and metaraminol.[3]

Low Molecular Weight Dextran

This agent has been widely recommended to improve peripheral perfusion by reducing the viscosity of blood, so preventing sludging or intravascular coagulation. It may achieve its effects by several mechanisms, by virtue of an osmotic effect causing hemodilution, by coating of red cells to reduce aggregation and by combination with fibrinogen to allow removal of the complex by the reticuloendothelial system.[100] Animal studies have shown its ability to reduce blood viscosity and hematocrit and increase blood volume,[101] to increase peripheral and portal flow[102] and to reduce acidosis and increase survival[103] more effectively than comparable volumes of blood or saline. In shocked humans, Suzuki et al.[104] have shown increased mobilization of sequestrated red cells at the periphery and Carey et al.[105] have demonstrated increased cardiac output, with decrease of the peripheral resistance and mean circulation time.

Maximum effect is obtained with blood levels of 1 gram of dextran per 100 ml. of the blood volume and this is achieved by administration of 500 ml. of a 50% solution in 1 to 2 hours.

Other Measures

Many other theoretically acceptable agents have been proposed and studied in animals although knowledge of their effects is not yet sufficient with most to extend their use to man. ATP[106,107] or mitochondrial preparations[108] have been found to increase survival rates in hemorrhagic shock possibly by improvement of oxidative phosphorylation but also possibly by their vasodilator and anticoagulant properties. Antihistaminics and 5-hydroxy-tryptamine antagonists improve the splanchnic circulatory changes in endotoxin shock[109] and 5-hydroxy-tryptamine antagonists reduce platelet aggregation.[74] Trasylol, an inhibitor of bradykinin, may have a place in the treatment of shock from pancreatitis and possibly septicemia.[72] In addition to its buffering action, THAM may produce

benefit from its osmotic activity causing plasma expansion[110] as may Mannitol. Finally, heparin has been advocated to reverse intravascular coagulation although little benefit has in fact been shown with its use.[111] □

SUMMARY AND CONCLUSION

The lethal effects of prolonged shock probably result from accumulation of toxic products secondary to poor tissue perfusion and anoxia with the development of anaerobic metabolic pathways. In the experimental animal, the major site of these changes is in the splanchnic viscera. The initially compensatory vasoconstriction in these parts to maintain perfusion of vital areas thus ultimately becomes a harmful response. Superimposed intravascular coagulation may be an important terminal change.

The initial treatment is directed to correcting the cause, by infusion of appropriate fluids, cardiac stimulation or antibiotic therapy. In many patients this will be sufficient to allow recovery; in others, cellular damage is so far advanced that no treatment is of avail. In a few cases, judicious ancillary treatment may allow survival. Vasopressor agents have a limited place particularly in cardiogenic and septic shock and occasionally in the emergency treatment of hemorrhage. Carefully controlled administration of vasodilator drugs may benefit advanced cases of hypovolemic shock. Evidence suggests that low molecular weight dextran might well specifically reverse sludging or intravascular coagulation. Further studies are required to define the safety and efficacy of many other proposed agents. It is considered that the selection and use of appropriate therapy in clinical patients can be more properly controlled only with adequate frequent hemodynamic measurements. □

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PROBLEMS IN THE SELECTION OF AN EXPERIMENTAL MODEL FOR THE STUDY OF HEMORRHAGIC SHOCK

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INTRODUCTION

The selection of an appropriate model for the study of hemorrhagic shock is often difficult. This difficulty in selection is in large part due to many inherent variables. Among these are:

1. Variables between species of experimental animals. These variations in species involve basic anatomic and physiologic characteristics, as well as the pharmacologic response.
2. Variables related to the technique and method used to bring about hemorrhagic shock, particularly in regard to administration of anesthesia, method of bleeding and method of return of reservoir blood to the animal.
3. Variable effects of seasonal and circadial influences.
4. Variable effects of adaptation to injury so that results of a second injury are unlike the effects of the first injury.

Certain aspects of each of these areas will be reviewed.

Variables Due to Species Difference

Difficulties arise when one attempts to transpose findings related to hemorrhagic shock from one animal species to another.[7,11] For example, if one uses pentobarbital anesthesia he may maintain a satisfactory airway in a dog, whereas in a rat or mouse, tracheal obstruction will occur from mucus produced by a catarrhal response to the agent. Species differences are suggested with particular reference to the liver and its vascular "sphincters."[3,6] It has been suggested that hepatic engorgement which develops in the dog when he is transfused, is related to such a difference in vasomotor response. Selkurt[5,6] has reported on the phenomenon of obstructed portal vein flow in shock. Using the squirrel monkey as a model, he has shown that hepatic and duodenal congestion, so strikingly seen in the dog, do not occur. This raises the question as to whether the origin of circulatory failure is peripheral in some species while central in others.

In addition to species differences a varying response can occur among different groups within the same strain of a species if there is a difference in the preceding history.

Among possible candidates for animal study, the rabbit is considered a poor animal for shock studies. The rabbit is difficult to anesthetize and it does not tolerate hypotension long enough to permit observation. Such observations have led to the speculation that hemorrhagic shock in the rat, hemorrhagic shock in the rabbit and hemorrhagic shock in the dog may be different entities.[6,7] Thus, the fact that collapse of circulatory homeostasis is observed in all animals after induced hypotension does not necessarily mean that the mechanisms producing shock are identical in every instance.

Brand has reported on the use of the cat as an experimental model in studies for hemorrhagic shock. Most impressive is the consistency of response to an applied stimulus during a period of inadequate tissue perfusion. The cat appears to be a convenient animal for a number of other reasons:

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1. Variations *within* the species are less significant than in the dog, since through the ages there has been far less breeding for anatomic peculiarities in the cat.
2. The "bacterial" status of the cat, that is to say the variations produced by endogenous bacteria, may be less complicated than the same conditions in the dog.
3. In the cat hepatic and intestinal response to hypotension is unlike that in the dog and resembles that in man in some respects.

In Brand's investigation,[1] selected male cats between two and four kilograms in weight were kept for a month at constant temperature in order to minimize seasonal effects. Diet was standardized. In these animals a rather uniform response developed to a stimulus of two hours of hemorrhagic hypotension at 40 millimeters of mercury followed by three hours at 45 millimeters of mercury. All animals died in respiratory arrest when the blood pressure eventually fell to 30 millimeters of mercury after about eighteen hours. These animals exhibited a gradual "straight line" drop in blood pressure during the period of study. Because of this constancy, duration of survival could be used as an index of therapy.

Variables Arising from Technique Used to Produce Hemorrhagic Shock

Loss of circulating blood volume represents a key factor in the general shock syndrome. Prevention of prolonged hemorrhagic hypotension therefore, goes directly to the core of the problem. With a prolonged period of deprived blood volume, all symptoms referable to the shock syndrome can be reproduced. Irreversibility may also be obtained. Procedures for the production of hemorrhagic shock generally fall into two categories:

A. Those in which a fixed volume is withdrawn regardless of changes in the blood pressure.
B. Those in which enough blood is withdrawn to reduce mean arterial pressure to a definite stabilized level. An example of the first procedure is represented by the work of Arimoto in 1945, where dogs were bled to a fixed percentage of predetermined blood volume. Ninety percent of the blood was reinfused 30 minutes later. This procedure was repeated five times at hourly intervals and produced death in 61% of 41 dogs. Wolcott, also in 1945, developed a method in which lethal bleeding volume (established by Wiggers in 1950[8] as 5% of body weight in the dog) was approximated and then a fixed proportion of blood volume was restored immediately. Using this technique blood pressure was variably restored to 40 to 60 millimeters of mercury, but then gradually declined until death in a period of considerable variability, 75 to 345 minutes. Hence, such a method does not generally produce consistent results.

A preferred technique generally is to bleed the animal until the blood pressure falls to a predetermined level, regardless of the blood loss required to produce this level. The assumption here is that reduction of blood pressure, at least roughly approximates the decrease of blood supply to the peripheral tissues. Two subdivisions can be delineated in this type of approach:

A. Fixed time schedule for a period of hypotension (Western Reserve method[8,9]). In this method arterial pressure is kept at 50 millimeters of mercury for 90 minutes then at 30 millimeters of mercury for 45 minutes.
B. Variable time schedule for a period of hypotension. In this the duration of the time schedule is adjusted to the individual tolerance of the animal.

A common adjunct to this method is employed when a definite percentage of the bleeding volume has been reabsorbed; the volume remaining in the reservoir is then reinfused intravenously. Arbitrary aspects of this method as noted in various reports are the levels of hypotension

which have been carried (35 to 70 millimeters of mercury), and the percentage uptake accepted as an end point (15 to 30% of blood volume).

Gurd[6,7] has reported a method which is an adaptation of that described by Zingg, Nickerson and Carter. Using dogs the level of hypotension is controlled by the level at which the blood collecting reservoir is set. First the systemic pressure of 40 millimeters of mercury is held for 60 minutes and then 70 millimeters of mercury for the next 30 minutes. At the end of this time the tubing to the reservoir is clamped for 90 minutes. The clamps are then released and the reservoir blood returned. In 31 animals so treated, the mortality was 100%, average survival time after transfusion being 13.2 hours. These results were obtained during summer months. In the winter, to cause a comparable severe stress, the first period had to be extended to 75 minutes and the second period to 45 minutes. Chloropromazine and hydrocortisone administered as single injections were reported to change this high mortality.

The problem of anesthesia is a serious and significant one for the experimental approach to shock. The following methods have been used:

A. 1 to 2 mgs. of morphine per kilogram of body weight given 1 to 2 hours before the start of the experiment.[2]
B. Sodium pentobarbital 35 mgs. per kilogram administered intraparenterally.[1]
C. Minimal dose of intravenous Sodium pentobarbital to permit cutdown and thereafter administered in very small amounts as needed.[6,7]
D. Urethane in the dose of 240 milligrams per kilogram is used by some investigators. Urethane is thought to produce less hemodynamic changes. Many other methods have been used.

The manner in which reservoir blood is returned to the animal can give rise to certain variables. The rate of return is important. If about 40% of the blood volume is returned in as little as five minutes, the heart is likely to fail. Blood sediment occurs in the reservoir bottle during the period of hypotension. When the red cells are resuspended before reinfusion, another variable is introduced. The temperature of reservoir blood is still another variable. Contamination of the blood may produce severe circulatory depression. Bell[6] has demonstrated that infusion of blood collected with nonsterile technique and stored seven to thirteen days causes a high output of 17 hydroxycortico steroids. In the same study, potassium and free circulating hemoglobin failed to produce an adrenal response.

Variation Related to Seasonal and Circadial Influences

In winter months, dogs are able to withstand oligemia and hypotension better than in summer months.[7] This could be an expression of cell adaptation to a variety of stresses including hemorrhage. Of particular importance in this regard is the circadial rhythm discussed by Halberg.[6,7] Problems presented by this particular rhythm are not met by performing experiments at the same time each day since the cycles are not precisely twenty-four hours in length and may be longer or shorter than this. Data on mortality must therefore be interpreted in terms of circadial rhythm. Environmental temperature and adaptation to injury also modify the effects observed. □

SUMMARY

From the above brief review it can be seen that great difficulty surrounds the structure of an experimental problem in this field, and that great care must be used in interpreting results. □

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METABOLIC ACIDOSIS IN SHOCK

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Metabolic acidosis has been defined as a pathophysiologic state in which the rate of accumulation of fixed endogenous or exogenous acids exceeds the capacity of the body mechanisms for acid excretion. If untreated, this process is accompanied by acidemia—an increased concentration of hydrogen ions in the blood with a resultant fall in pH. Acidemia is also accompanied by a decrease in blood bicarbonate concentration.

Metabolic acidosis due to an excessive rate of production of organic acids such as the betahydroxybutyric acids in diabetic ketoacidosis has been known for quite some time. Clinicians, however, have only recently become interested in other forms of metabolic acidosis. The metabolic acidosis occurring in shock has been related in some ways to the development of lactic acidosis.

The accumulation of lactic acid with exercise is a normal process attributed to anaerobic metabolism. That is to say, the increased need for glucose utilization coupled with the inability of the vascular system to furnish oxygen to the enzyme systems, results in an accumulation of lactic acid.

Huckabee in 1961 first described the clinical syndrome of lactic acidosis associated with hypotension, hyperpnea, dyspnea, and stupor resulting from hyperlactatemia.

Peripheral circulatory failure resulting from decreased cardiac output as seen in hemorrhagic or endotoxin shock or following a cardiac arrest, becomes the causative factor of tissue hypoxia. In the normal individual, the heart and liver are responsible for detoxifying the accumulated lactic acid. Late in the state of hemorrhagic shock, or much earlier following a cardiac arrest, the liver can no longer detoxify lactic acid and, in fact, contributes to the acidosis.

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Hypotension associated with cardiovascular collapse such as that seen in cardiac arrest, results in a sudden, severe metabolic acidosis.

Litwin has shown that the reactivity of vascular smooth muscle and the heart muscle become markedly decreased with the accumulation of lactic acid. Vasopressors such as epinephrine and norepinephrine are often unable to reverse this kind of hypotension until acidosis is corrected. They, in fact, aggravate the situation because further vasoconstriction prevents adequate perfusion of tissue and causes further increase in lactate formation. This accounts for the rationale behind the use of vasodilators and volume replacement in shock and shock-like states. In our experience other drugs such as calcium chloride, isuprel, xylocaine, and quinidine have also been poorly effective until acidosis has been at least partially corrected.

Animal studies reported by Darby showed that the action of vascular and cardiac vasopressors and isometric contracting agents can be improved when acid-base balance is corrected simultaneously. Myocardial contractility is reduced due to a lessened response to the sympathoadrenal stimulation of the catecholamines by an acidotic myocardium. This in turn reduces cardiac output.

The 90% of bodily energy normally derived via the tricarboxylic acid cycle from the oxidative metabolism of glucose becomes unobtainable in the presence of total anoxia. Pyruvic acid, potentially capable of producing about 33 moles of energy-rich phosphate bonds would

rather, in the presence of anoxia, be reduced to lactic acid. Thus lactic acid, because of its ability to pass rapidly through the cell membrane, results in a rapid rise of the normal extracellular level of 15% to a level of several hundred mg%. While the patient remains in total asystole or in hemorrhagic shock with marked vasoconstriction, only a moderate rise occurs in the extracellular concentration of lactic acid. However, as soon as circulation is re-established these accumulated metabolites suddenly become released into the systemic circulation in high concentration. This becomes quite evident when the pH of venous blood following a cardiac arrest is compared with that of arterial blood.

Hypothetically, in severe acidosis the following major events appear to occur: As previously mentioned, the presence of acidosis markedly depresses the myocardial energy metabolism. Such a deterioration of the myocardial expulsive power occurs rapidly and may significantly contribute to a markedly lessened cardiac output.

The presence of systemic acidosis may cause the arteriolar sphincters to lose tone. The ultimate effect is capillary stasis and increased capillary hydrostatic pressure. This increased pressure combined with a loss of capillary integrity, results in the pooling of large amounts of fluid in the tissues. Such losses of plasma can be demonstrated by the drop in systemic albumin as well as the rise in hematocrit which occurs in shock. Such a pooling of fluid in the tissues further contributes to capillary stasis, leading to a greater acidosis and the initiation of a vicious cycle. The greater the degree of stasis in peripheral tissue, the less will be the amount of blood that is returned to the heart. This leads to a further decrease in cardiac output, resulting in even greater degree of tissue hypoxia.

Respiratory acidosis is occasionally seen in association with metabolic acidosis. This is somewhat uncommon, however, since metabolic acidosis is usually accompanied by hyperventilation which tends to produce respiratory alkalosis.

In order to differentiate the form of acidosis or the relative proportion of mixed forms present, one has a number of studies at hand which can be of help.

First, is the *blood pH*—this is a term first defined by Sorenson in 1909 as the negative log of the hydrogen ion concentration. This concept has long posed a difficult concept to most physicians. In the management of early shock or cardiac arrest the pH is sometimes lagging and rarely helpful in the management. *A pCO_2 level*, however, can be most helpful in distinguishing decreased ventilation and the accumulation of partial pressure of CO_2.

Actual Bicarbonate is the bicarbonate concentration in plasma, in meq/liter, measured in blood drawn under anaerobic conditions. Actual bicarbonate level, is affected by both respiratory and metabolic balance. There are two ways to get over this difficulty:

1. Bicarbonate concentration in plasma can be equilibrated at a pCO_2 of 40 mm Hg and with oxygen at full saturation of hemoglobin. This measurement is known as the *standard bicarbonate level*.
2. A second method is to calculate the *buffer base level*. This is a very helpful measurement, first introduced in the literature by Singer and Hastings in 1948. Buffer base is a measurement of the sum of the systemic buffer ions, mainly bicarbonate and proteinate ions measured in Meq/liter.

Although the bicarbonate fraction is altered by a respiratory disturbance, as mentioned in discussion of actual bicarbonate, the protein fraction is affected in an inverse manner so the actual total is unchanged. Therefore buffer base has the advantage of distinguishing clearly between respiratory and metabolic imbalance, a distinction which actual bicarbonate does not have. Buffer base has one disadvantage in that its protein component is mainly hemoglobin. In the not too uncommon situation of a shock patient with a hemoglobin of less than 10.0 gm. this figure can still be calculated.

Another new concept, not fully accepted in the literature, and given at most a line or two in current textbooks is the concept of *base excess*. In this hospital we have found it an ideal way to follow the patient in acidosis. We have applied the expression as either "base excess" or "base deficit." Measured in Meq/liter base excess is defined as zero for blood at 7.40 and pCO_2 of 40 mm Hg. Positive values indicate an excess of base (or a deficit of fixed acids). Negative values indicate a deficit of base (or an excess of fixed acid).

The normals of the above determinations are arterial pH of 7.40 and venous pH of 7.42. This latter is markedly lowered in the case of decreased circulatory perfusion of the extremities, such as in severe shock or during and following a cardiac arrest. In these situations accuracy of management can be achieved only by the use of arterial blood samples.

The normal arterial pCO_2 is 40. This is markedly increased in respiratory depression and chronic lung diseases. It is decreased in hyperventilation.

The normal standard bicarbonate level (or actual bicarbonate level when the pCO_2 is 40) is 24.5 to 27 mg/l. This can be shown from the Henderson-Hasselbach equation.

The normal buffer base level is 45–55 and base excess is 0 Meq/liter. Just how does one make use of such information in determining the quantity of buffer replacement? There are three rules of thumb which we have found helpful.

1. Base excess $\times$ Kg $\times$ 0.3 = cc of $NaHCO_3$ required for replacement.
2. Total CO_2 (actual bicarbonate plus 0.03 $\times$ pCO_2) at present subtracted from the desired CO_2 level $\times$ .6 $\times$ Kg. = the Meq of $NaHCO_3$ required for replacement.
3. .75 cc $NaHCO_3$/Kg raises CO_2 1 Meq/liter.

Although in this discussion replacement is given in terms of $NaHCO_3$ therapy, THAM (tris hydroxymethyl Amino Methane) would appear to be a better agent for the treatment of acidosis. THAM has the outstanding ability to buffer intracellularly, as well as extracellularly. It is reported that 35 to 50% of the action of THAM is at the intracellular level and there it is capable of correcting acidosis without regard for the respiratory action. Also THAM offers a method of correcting urinary acidosis while achieving excellent osmotic diuresis.

Similar results might theoretically be expected if sodium bicarbonate or lactate were given in combination with mannitol. These agents, if used together, could correct the systemic acidosis as well as achieve osmotic diuresis. Should such therapy be necessary for long periods, however, significant problems could occur. The sodium present in the large quantity of lactate or bicarbonate buffer needed to correct the acidosis could well cause an overloading of the circulatory system and congestive failure. Lactate and bicarbonates are poor buffers when compared with THAM and act only to correct extracellular acidosis, thus intracellular equilibration may be unduly delayed when these buffers are used. □

SUMMARY

The accumulation of acid metabolites can be shown to produce a major obstacle in the treatment of certain forms of shock. Our experience parallels that reported by Darby. We believe that close attention to this problem will improve the results in shock which is associated with or produced by cardiac arrest. □

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□

REVIEW ARTICLE

WIENER G-FUNCTION ANALYSIS AS AN APPROACH TO NONLINEAR CHARACTERISTICS OF HUMAN PUPIL LIGHT REFLEX

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INTRODUCTION

In attempting to describe mathematically or to characterize the "Black box" input-output behavior of the human pupil light reflex, we investigated three different basic formulations of the system. The Wiener G-functionals, a recently developed mathematical characterization of systems, will be discussed in detail but we will first briefly present two other, more standard, approaches to the problem, describing functions and heuristic modeling. Neglecting the experimental details—some of which will be presented later—let us assume that the experimenter has available transducers capable of generating input light stimuli as waveforms of arbitrary time dependence and monitoring an analog voltage proportional to the output, pupil area of a normal awake human subject.

The linear transfer function description attempts to represent the input-output behavior by a linear system. Stark and Sherman[1] first used this method and were able to predict the frequency of high loop-gain, instability oscillations.[2] These studies have been extended in a quantitative manner and are in part presented here. Figure 1 shows typical input-output records of the human pupil response to sinusoidally varying light; gain and phase vs frequency curves for this class of experiments are seen in Figure 2. The asymptotic slope of the gain vs frequency curves indicates a system of approximately third order. One is immediately suspicious of any linear model since the gain curves change appreciably with stimulus input amplitude. Note, however, that the phase vs frequency curves are almost identical for different stimulus amplitudes. It is this very strong behavioral constraint in the pupil light reflex system which enabled Stark and Cornsweet[2, 3] to use a linear model to predict correctly the closed loop oscillation frequency in their studies of the pupil.

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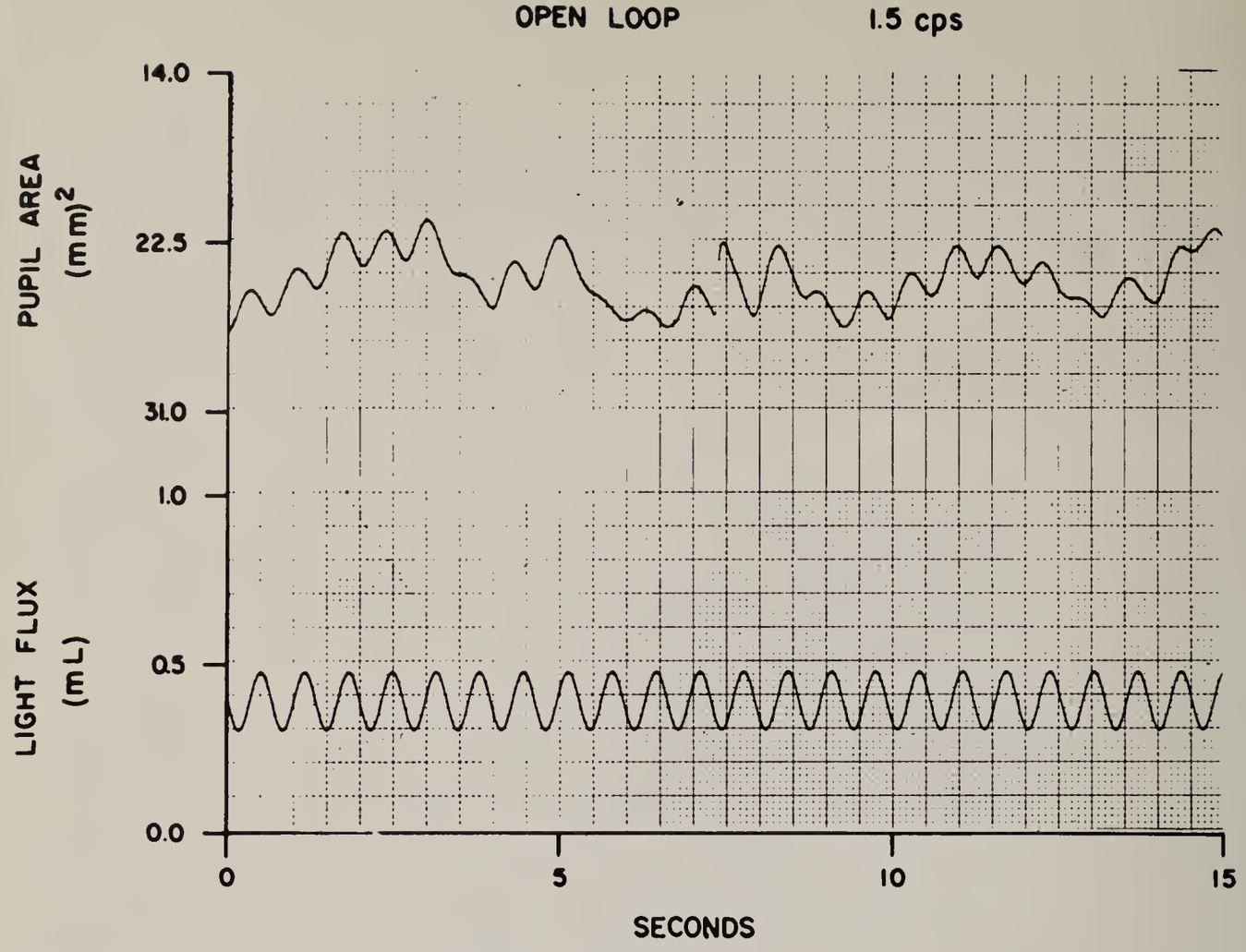


Fig. 1.—Pupil response to steady state light flux changes.

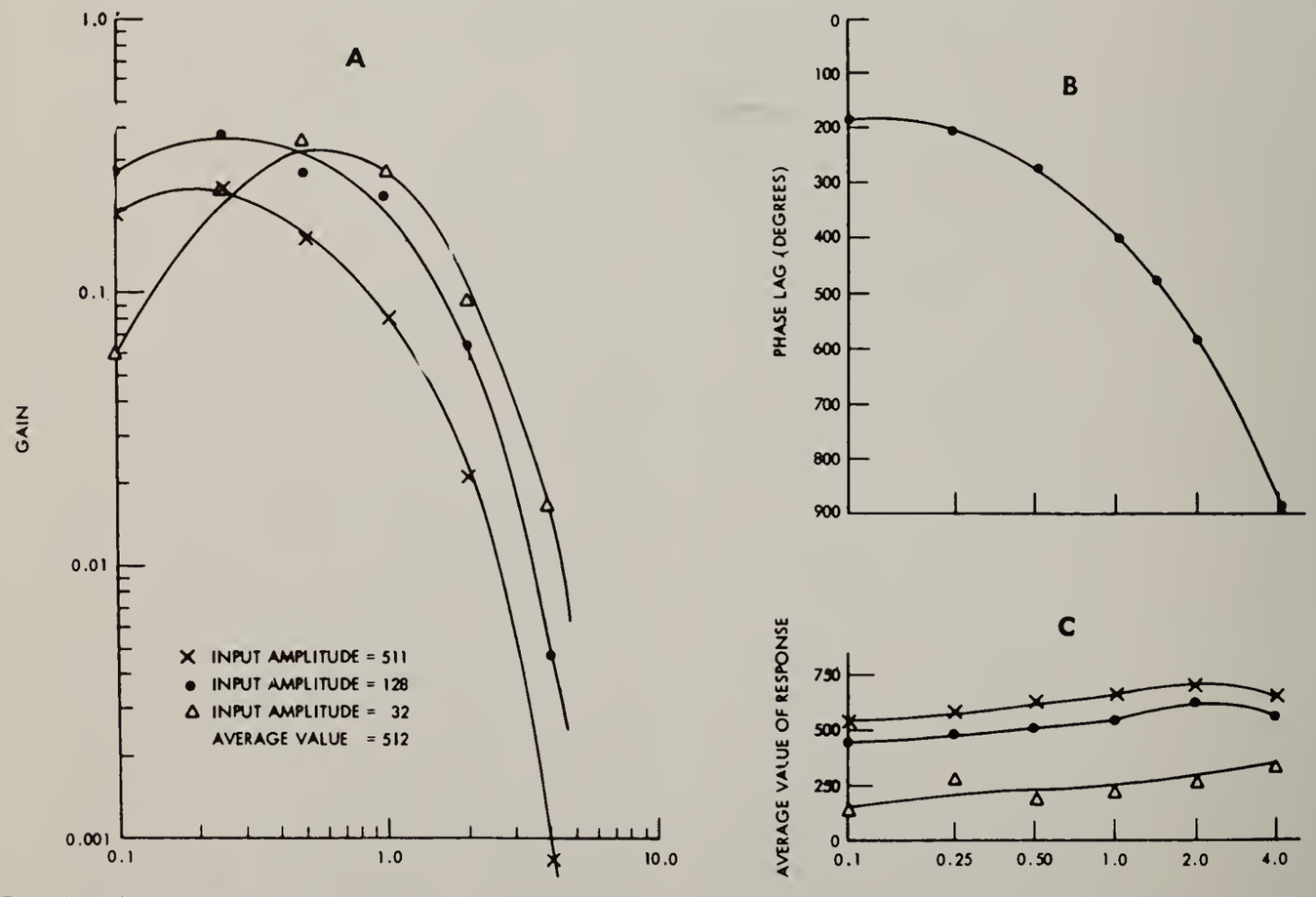


Fig. 2.—Sinusoidal steady state response of pupil system to light as a function of frequency with stimulus amplitude as a parameter.

In order to present more clearly the pupil nonlinearities, we have plotted in Figure 3 the gain and phase vs input amplitude with frequency of stimulation as a parameter. Since the gain vs amplitude curves at the two stimulation frequencies are appreciably different shapes, the pupil system cannot be represented simply as a no-memory nonlinearity followed by a linear system. Therefore it is impossible to describe the system in

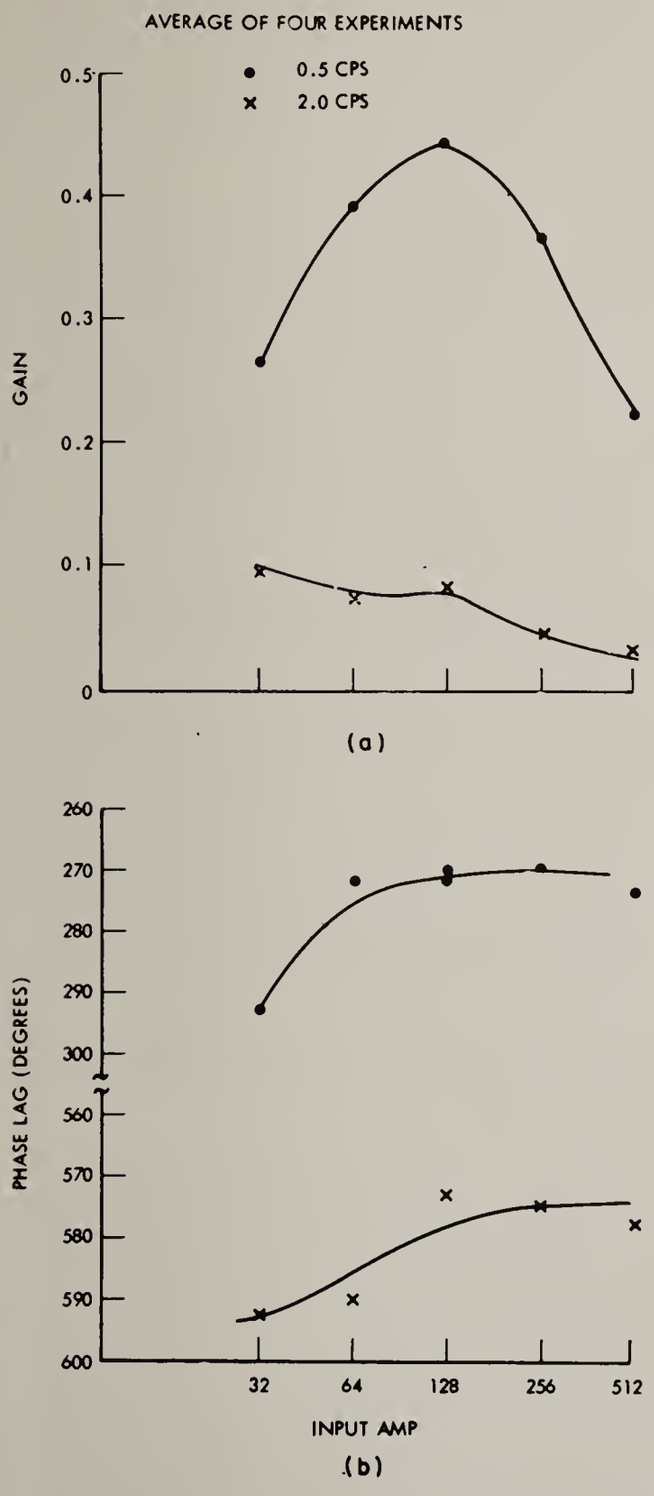


Fig. 3.—Sinusoidal steady state response of pupil system to light as a function of stimulus amplitude with frequency as a parameter.

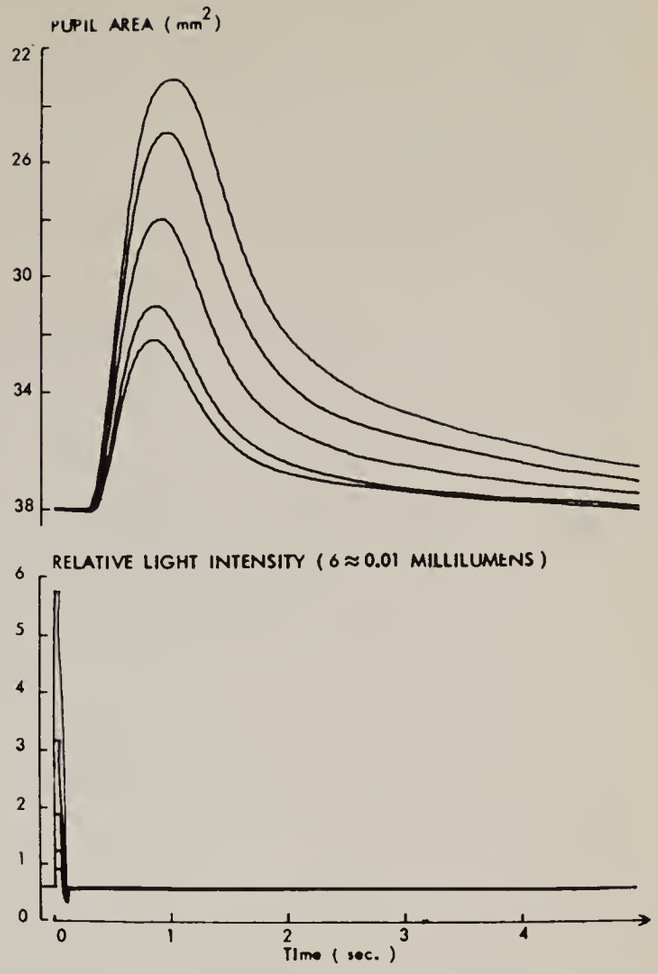


Fig. 4.—Human pupil responses to short pulses of light.

simple describing function theory. It can, however, be shown that the previous sinusoidal response data is consistent with a model comprised of some combination of cascaded linear systems separated by no-memory nonlinearities.[4]

An extremely popular and often useful modeling technique is to perform a series of experiments, usually with transient stimuli. One acquires experience with the system which coupled with other information one might think pertinent—including preconceived notions—thereby formulates a time invariant, nonlinear heuristic model. The model's primary purposes are to describe the input-output behavior and approximate, at least in some sense, the topology of the signal flow in the real physical system.

In the case of the pupil light reflex, there are several easily observed nonlinear effects. Typical pulse responses are seen in Figure 4. In addition to the basic wave shape, one immediately observes that a substantial amplitude compression

exists fairly early in the signal processing system since the amplitude of response varies over about a factor of three while the input signal changed over a factor of thirty-two and the response shapes are extremely close when all the responses are normalized to the same peak-to-peak height.

Figure 5 illustrates another important nonlinearity—asymmetry. This nonlinearity seems to show its effect especially when the stimuli approach the small signal region.[5] Because of this some investigators have raised serious objections to the use of methods which attempt to linearize the pupil system in order to carry out a quantitative analysis.[4,6] The model illustrated in Figure 6 represents one attempt to form a heuristic model of the pupil light reflex. In such model making one must choose between making the model more complex to incorporate some experimental data or settling for a simpler model, incomplete but more understandable. We will not stress this heuristic method of characterization, but instead proceed to the Wiener method, which lacks close connection with possible physiological processes, but is a general mathematical description capable of

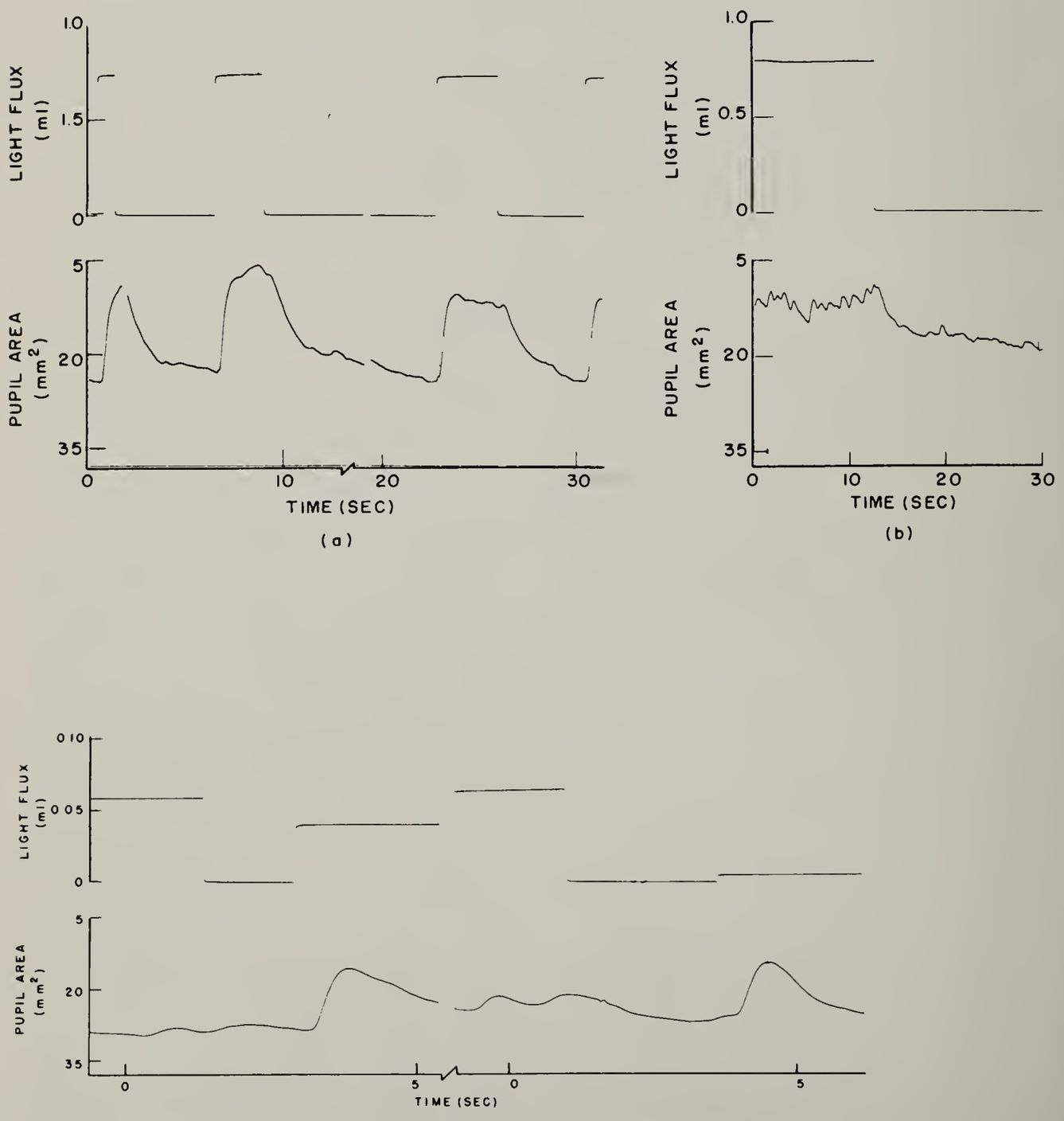


Fig. 5.—Pupil light reflex showing asymmetrical nonlinearity effect.

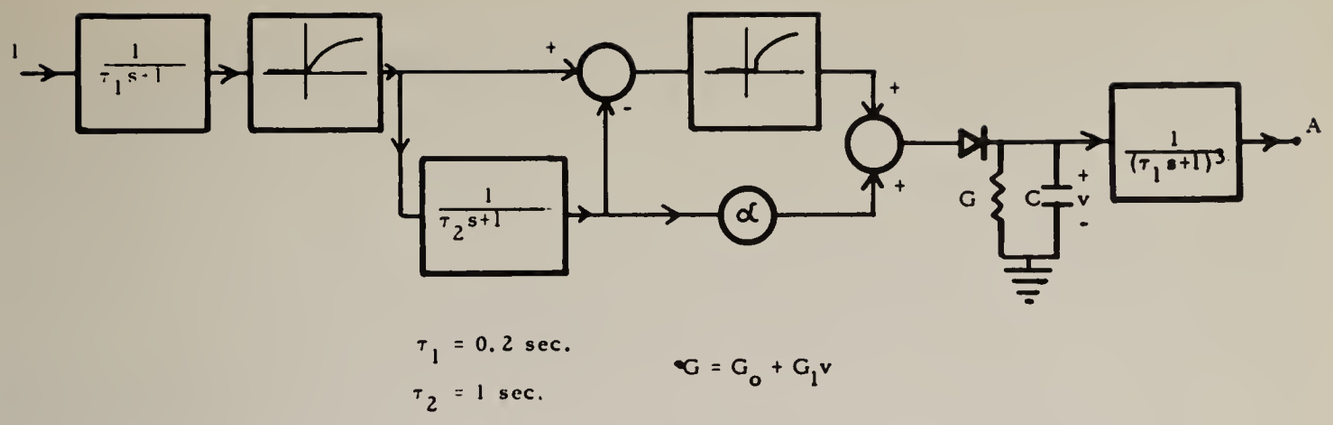


Fig. 6.—Heuristic model of human pupil light reflex.

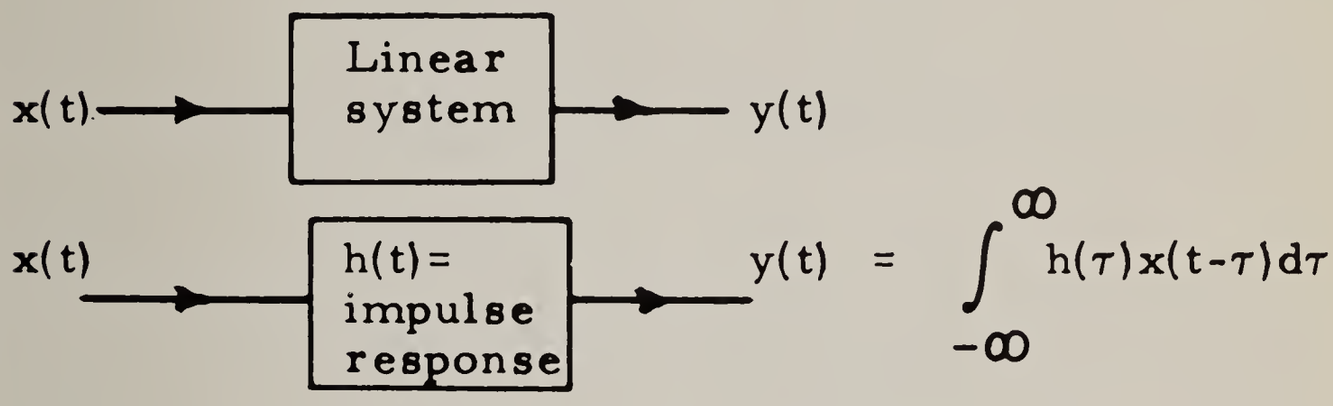


Fig. 7.—Representation of linear system by its impulse response h(t).

representing an extremely wide class of systems.

This characterization, the main subject of the present paper, is essentially a Volterra functional expansion of the pupil system with kernels $h_0(\,)$, $h_1(\,)$, $h_2(\,)$, etc.*

Output and input are related as follows:

$$y(t)=\int h_1(\tau)\times(t-\tau)d\tau+\int\int h_2(\tau_1,\tau_2)\times(t-\tau_1)\times(t-\tau_2)d\tau_1 d\tau_2+\cdots \qquad \text{(Eq. 1)}$$

The computationally difficult task in this characterization is the determination of the kernels $h_i(\tau_1, \tau_2, \tau_i)$, $i=1, \ldots n$. An even more profound question which arises in this method is whether any physical significance or interpretation can be given the kernels—even if they could be found—or are we to pay the price for mathematical elegance by an inability to interpret our results? Do the kernels have any other identifiable significance in addition to their being the magic kernels that simply crank out the correct output when introduced into the Volterra expansion? First, let's describe two analytic procedures for obtaining the kernels and then present the experimental results pertinent to each theoretical method.

*$h_o(\,)$ is the zeroth order kernel and represents the constant DC level with zero input and is ignored in the remainder of our paper.

Measurements by Use of Random Signals

A linear system as shown in Figure 7 is represented in the time domain by its impulse response function $h(\tau)$. The output $y(t)$ is related to the input $x(t)$ by the superposition or convolution integral.

$$y(t) = \int h(\tau)x(t - \tau)d\tau \quad \text{(Eq. 2)}$$

One method of experimentally computing $h(\tau)$ is to excite the linear system with white noise, that is

$$\varphi_{xx}(\tau) = Au_0(\tau)$$

where u_0 is the Dirac delta function, and to crosscorrelate the output and input.[7] It can be seen that

$$h(\tau) = (1/A)\varphi_{yx}(\tau). \quad \text{(Eq. 3)}$$

The representation of a general nonlinear system is shown in Figure 8. If the system under study can be suitably approximated by only one of the Volterra terms of the—in general—infinite expansion, then a simple technique exists for determining the kernel of that term.[8] Figure 9 illustrates the computation of h_n by multi-dimensional crosscorrelation between output and input when the input is white Gaussian noise. The computation of the isolated high order Volterra kernel is a direct extension of the case of a linear system. It should be noted that although we cannot determine the values of $h_n(\tau_1, \ldots, \tau_n)$ along any curve where any two τ^1s are equal with this method, one can practically assume continuity of h_n to find such values if needed.

An extremely serious drawback to the Volterra series is that it is not an *orthogonal* functional expansion. Thus if the first n terms have already been computed, then the entire computation must be repeated if n+1 terms are desired. Another important defect of the Volterra method is that computation of the non-isolated kernels is no longer a simple task but involves the solution of a set of simultaneous integral equations.[14]

In much the same way that Legendre polynomials are formed to make an orthogonal function set useful for curve fitting, so can a set of orthogonal functionals for nonlinear system characterization be formed. This was first done by Norbert Wiener, whose work was further simplified by Y. W. Lee and his coworkers.[7] Omitting details of this work, we can say that the general measuring scheme in the determination of Wiener G-functionals is identical to that of determining isolated Volterra kernels. The Wiener representation is illustrated in

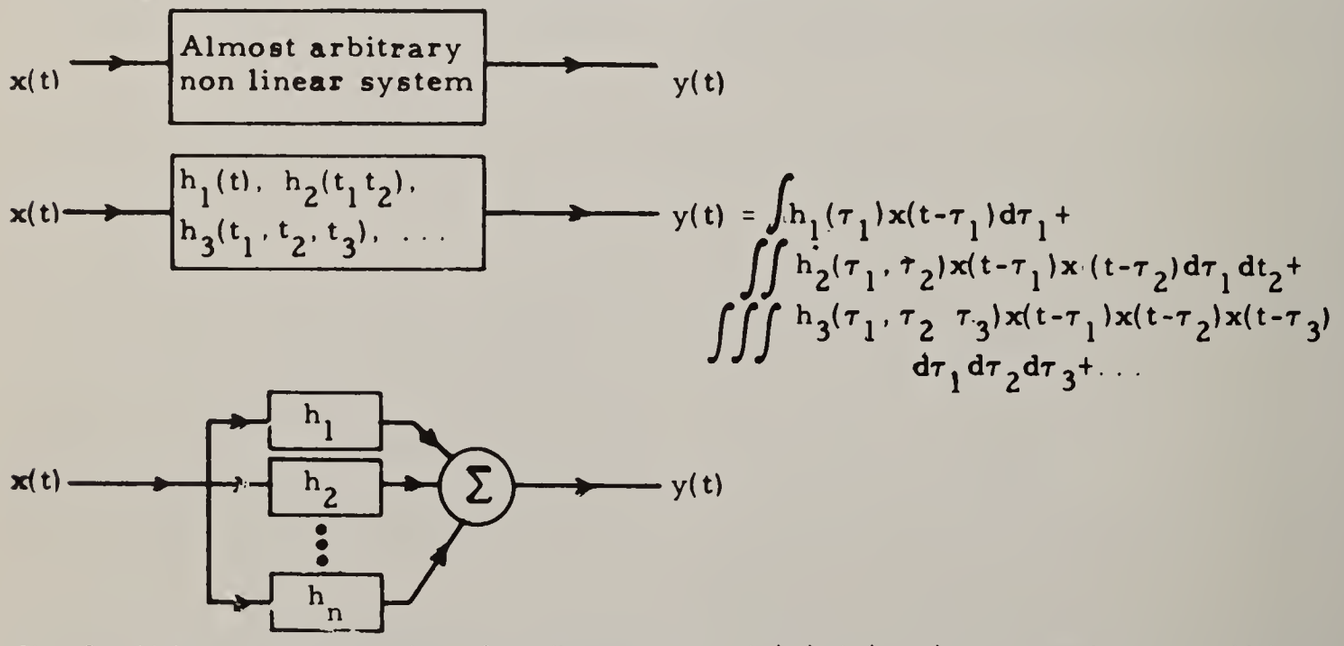
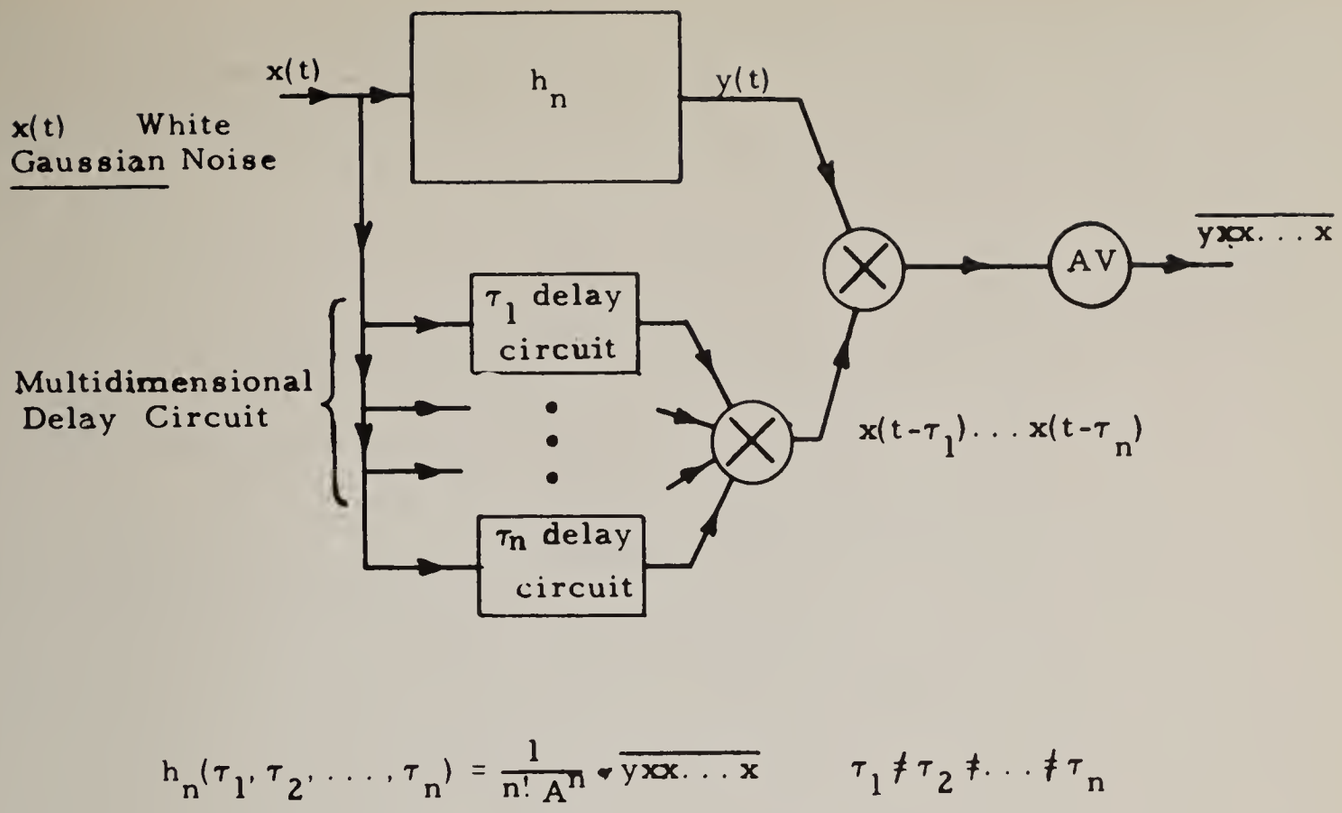


Fig. 8.—Volterra representation of nonlinear system. $h_1(\tau_1)$, $h_2(\tau_1,\tau_2)$, etc. are known as Volterra kernels of system.



$$h_n(\tau_1, \tau_2, \ldots, \tau_n) = \frac{1}{n!\,A^n} \cdot \overline{yxx\ldots x} \qquad \tau_1 \neq \tau_2 \neq \ldots \neq \tau_n$$

Fig. 9.—Measurement of *isolated* hi-order kernel.

Figure 10 where the experimentally determined g_i are used for forming the Wiener G-functional expansion.

After using a Legendre series for minimal square curve fitting, one may go back and, by merely collecting appropriate terms, form the algebraic polynomial of the form:

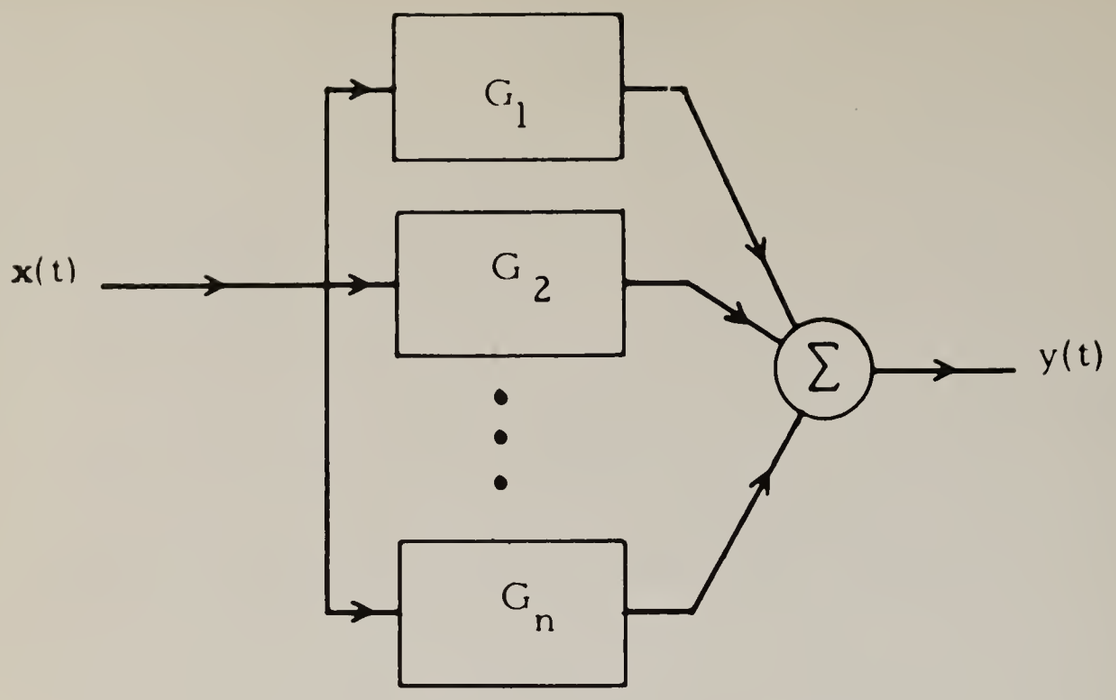
$$y = a_0 + a_1x + a_2x^2 + \cdots \qquad \text{(Eq. 4)}$$

In a similar manner, after one has first determined the G-functionals—because of their computational convenience—it is a relatively simple matter to perform some simple integration and collection of terms in order to form the corresponding Volterra expansion. Since a finite G-functional expansion represents the best minimal squares approximation to the system, the derived Volterra expansion must, for the constrained maximum order of the expansion, also represent the best system characterization in the mean square sense.

Continuing to relate ordinary power series expansions to functional expansions we see that just as the polynomial series is more amenable to interpretation than the corresponding orthogonal expansions, so the individual terms of a Volterra expansion are more easily interpreted than the G-functionals themselves. We will examine some of the properties of individual Volterra kernels by applying special transient inputs to the system.

It should be noted that the condition for use of white noise is incompatible with actually performing the necessary measurements experimentally since such an input has infinite variance and it can be shown that as a consequence all of the needed averages (high order correlation functions) will also have undefined variances, not to mention the infinite power content of such a signal. The effect of band-limited noise on the measurement will be seen later.

A Volterra or Wiener G-functional characterization can be used to represent a wide class of nonlinear time invariant finite memory systems. The more theoretical aspects such as the exact, necessary and/or sufficient conditions for this type of characterization to converge will not, and in some cases, cannot be derived.



$$G_1\ g_1,\ x(t) = \int g_1(\tau)\, x(t-\tau)\, d\tau$$

$$G_2\ g_2,\ x(t) = \iint g_2(\tau_1, \tau_2)\, x(t-\tau_1)\, x(t-\tau_2)\, d\tau_1\, d\tau_2 - A\iint g_2(\tau, \tau)\, d\tau$$

$$G_3\ g_3,\ x(t) = \iiint g_3(\tau_1, \tau_2, \tau_3)\, x(t-\tau_1)\, x(t-\tau_2)\, x(t-\tau_3)\, d\tau_1\, d\tau_2\, d\tau_3 - 3A\int \left[\int g_3(\tau_2, \tau_2, \tau_1)\, d\tau_2\right] x(t-\tau_1)\, d\tau_1$$

Fig. 10.—Orthogonal Wiener G functionals.

Measurements in the Time Domain

Whereas the previous analysis with random inputs gave rise to a nice mathematical framework, the work now to be presented lacks that foundation but obtains for us some badly needed insight into high order kernels. If a linear system is excited by an impulse, the response is by definition the kernel or impulse response function of the linear system. The generalization of this type of input in order to determine higher order kernels than the first consists of presenting multipulse stimuli where time t and the relative spacing of the pulses are the independent variables tracing out the high order kernels. The method is not orthogonal in the sense that the entire procedure must be repeated if we wish to extend the maximum order of the approximation. A more serious objection to the method is that we will form the Volterra characterization to exactly agree with the real system for one very specialized input and if the system contains more kernels than we assume in the analysis, the derived characterization might prove very poor for other classes of input. The advantage of a random input to characterize the system is that one essentially obtains the best characterization over a wide class of inputs although the representation might not be very good for a particular input if the Volterra series has been truncated. We will treat in detail the case of a double pulse stimuli.

In this case the system is to be approximated by the first two terms of a Volterra series. The word "approximate" could be misleading since we are not using any criterion of goodness de facto because the

method is going to make h_1 and $h_2(\tau_1,\tau_2)$ be such that they completely describe the double pulse experiment. The approximation is that the system is being represented for all inputs as the first two terms of a Volterra expansion. The three pertinent experiments necessary for this method are tabulated below:

Experiment #1: $x(t) = Au_0(t)$
Therefore: $y_1(t) = Ah_1(t) + A^2h_2(t,t)$

Experiment #2: $x(t) = Au_0(t - T)$
Therefore: $y_2(t) = Ah_1(t - T) + A^2h_2(t - T, t - T)$

Experiment #3: $x(t) = Au_0(t) + Au_0(t - T)$
Therefore: $y_3(t) = Ah_1(t) + Ah_1(t - T) + A^2h_2(t, t) + A^2h_2(t - T, t - T) + 2A^2h_2(t, t - T)$

where $h_2(\tau_1, \tau_2) = h_2(\tau_2, \tau_1)$ has been used.
It is easily seen that

$$y_3 - y_1 - y_2 = 2A^2h_2(t, t - T)$$

and that

$$-y_3\Big|_{T=0} + 4y_1 = 2Ah_1(t).$$

The term in the output of experiment #3, $h_2(t,t-T)$, represents a nonlinear interaction between the two stimuli pulses. Note that if $h_2(t,t-T)=0$ for $T\neq 0$, then for $T\neq 0$ the system would obey what we might call time superposition in the sense that we could add the responses due to each stimulus pulse presented separately and correctly predict the output when both were presented together. Thus $h_2(\tau_1=\tau_2)$ being nonzero off its main diagonal $(\tau_1=\tau_2)$ line indicates the degree of time nonlinear interaction between different portions of the input signal. A no-memory squarer followed by an arbitrary linear system and possibly shunted by another linear system has this exact property. Any no-memory nonlinearity followed by a linear system obeys the principle of time superposition. In this general case the order of the required Volterra expansion is determined by the order of the nonlinearity and every kernel is zero everywhere except where $\tau_i=\tau_j$; along these lines the kernel is a wall of impulses. Thus the magnitude of the kernels off their diagonals indicate the extent of the nonlinear interaction in time.

Futher Topics in Quantitative Measurement; Cascading and Bandwidth Effects

If an isolated Volterra kernel $h_2(\tau_1, \tau_2)$ is followed by a linear system $h(\tau)$ the following relation between input $x(t)$ and output $y(t)$ is readily derived:

$$y(t) = \int\int [h_2(\lambda_1 - \xi, \lambda_2 - \xi)h(\xi)d\xi] \times (t - \lambda_1) \times (t - \lambda_2)d\lambda_1 d\lambda_2. \qquad \text{(Eq. 5)}$$

The new kernel is therefore

$$h_2(\lambda_1, \lambda_2) = \int h_2(\lambda_1 - \xi, \lambda_2 - \xi)h(\xi)d\xi. \qquad \text{(Eq. 6)}$$

For any given (λ_1, λ_2) this can be seen to be just a weighted average of the original h_2 along lines parallel to the main diagonal $\lambda_1 = \lambda_2$; thus we are in effect smearing out h_2 along lines parallel to $\lambda_1 = \lambda_2$.

If an isolated Volterra kernel h_2 is preceded by a linear system h, the following relation between input and output is true:

$$y(t) = \int\int\left[\int\int h_2(\lambda_1, \lambda_2)h(\tau_1 - \lambda_1)h(\tau_2 - \lambda_2)d\lambda_1 d\lambda_2\right] \times (t - \tau_1) \times (t - \tau_2)d\tau_1 d\tau_2. \quad \text{(Eq. 7)}$$

The new second order kernel is therefore

$$\int\int h_2(\lambda_1, \lambda_2)h(\tau_1 - \lambda_1)h(\tau_2 - \lambda_2)d\lambda_1 d\lambda_2 \quad \text{(Eq. 8)}$$

which is simply a two dimensional convolution integral. This will clearly smear the original h_2 both parallel and perpendicular to the $\lambda_1 = \lambda_2$ diagonal line.

In conclusion we see that a linear system preceding a nonlinear one will generally increase the nonlinear interaction time whereas the linear system following the nonlinear one will only increase the overall memory of the system.

Using some of the above results it is interesting to ask: is it possible to find two linear systems, one of which will precede an h_2 and the other which will follow the same h_2 so that the overall behavior of the two resulting systems are identical? The easiest route to a solution is to first define the multi-dimensional Laplace transform as

$$F(s_1, \ldots, s_n) = \int \cdots \int f(t_1, \ldots, t_n)e^{-s_1 t_1} \cdots e^{-s_n t_n} dt_1 \cdots dt_n. \quad \text{(Eq. 9)}$$

Let $h_2(\tau_1, \tau_2) \leftrightarrow H_2(s_1, s_2)$ and $h(\tau) \leftrightarrow H(s)$, $h'(\tau) \leftrightarrow H'(s)$ define the nonlinear system and the two linear systems respectively with h' denoting the one preceding h_2. That is, is it possible for us to find an $h(\tau)$ and $h'(\tau)$ such that the two configurations of Figure 11 are equivalent. Using the previously derived material it is not difficult to show that the basic condition for the systems of Figure 11 to be equivalent is that

$$H_2(s_1, s_2)H(s_1)H(s_2) = H_2(s_1, s_2)H'(s_1 + s_2) \quad \text{or}$$
$$H(s_1)H(s_2) = H'(s_1 + s_2) \quad \text{(Eq. 10)}$$

for all values of s_1 and s_2. The only nontrivial $H(s)$ and $H'(s)$ for which this is true is $H(s) = H'(s) = e^{-Ts}$ which represents a time delay of T seconds. This result should not be surprising given the previously developed interpretations concerning the difference between linear systems preceding and following nonlinear ones.

We now turn our attention to a seemingly more pressing problem of measurement. Functional analysis theory requires white noise whereas statistical theory tells us that we have an impossible task in obtaining reliable correlation estimates not to mention the impossibility of generating white noise from energy considerations. It will turn out, as expected, that we will only have to use noise of a bandwidth of an order of magnitude greater than the system's bandwidth in order to make the previously stated equations for the determination of Wiener G-functionals valid for all practical purposes. We call noise of this bandwidth adequate bandwidth noise. Our basic problem is illustrated in Figure 12 in which the system we are trying to characterize is denoted by S and only signals $y(t)$ and $x(t)$ are available.[11] $h(t)$ is the impulse response of a lowpass filter which filters the imaginary white Gaussian noise $x_w(t)$ to $x(t)$ the real input into the system. Each kernel of S' and S are related by

$$h'_n(\tau_1, \ldots, \tau_n) = \int \cdots \int h_n(\lambda_1, \ldots, \lambda_n)h(\tau_1 - \lambda_1) \cdots h(\tau_n - \lambda_n)d\lambda_1 \cdots d\lambda_n \quad \text{(Eq. 11)}$$

which is merely the generalization of Equation 8. By taking the multi-dimensional Laplace transform of both sides and dividing through $H(s_1)\ldots H(s_n)$ and then taking the inverse transform it is, at least in principle, possible to get h_n thus characterizing S if we knew h'_n. Characterization of S' by h'_n however involves the computation of

$$\varphi y x_w x_w \ldots x_w(\tau_1, \ldots, \tau_n) \qquad \text{(Eq. 12)}$$

which cannot be done since $s_w(t)$ is unavailable in any physical sense. However $\varphi y x_w \ldots x_w$ is related to $\varphi y x \ldots x$ by

$$\varphi xy \ldots x(\tau_1, \ldots, \tau_n) = \int \ldots \int \varphi y x_w \ldots x_w(\xi_1 + \tau_1, \ldots, \xi_n + \tau_n) \cdot h(\xi_1) \ldots h(\xi_n) d\xi_1 \ldots d\xi_n. \qquad \text{(Eq. 13)}$$

The above becomes obvious after we consider the case for a second order kernel as follows:

by definition $\varphi_{yxx}(\tau_1, \tau_2) = \overline{y(t) \times (t - \tau_1) \times (t - \tau_2)}^{t}$,

and $x(t - \tau) = \int h(\xi) x_w(t - \tau - \xi) d\xi$,

therefore:

$$\varphi_{yxx}(\tau_1, \tau_2) = \int\int h(\xi_1) h(\xi_2) \overline{y(t) x_w(t - \tau_1 - \xi_1) x_w(t - \tau_2 - \xi_2)}^{t} \cdot d\xi_1 d\xi_2 \qquad \text{(Eq. 14)}$$

and hence, the result previously stated is proved.

We can again use multi-dimensional Laplace transform techniques to find $\varphi y x_w \ldots x_w(\tau_1, \ldots, \tau_n)$ if desired.

. In practical measurements, we use adequate bandwidth noise so that multi-dimensional Laplace transforms and their inversions prove to be unnecessary. The effect of lesser bandwidth of the input can, however, be quantitatively estimated by reference to Equations 11 and 13—i.e., Equation 11 shows that the obtained correlation functions are really the result of convolving the desired correlation functions with the low pass filters impulse response. Equation 13 shows the corresponding property for the kernel of interest.

Experimental Methods

An infrared reflecting pupillometer was used to continuously record the pupil area. A glow modulator, voltage-to-light transducer, was used as stimulus generator in an optical arrangement which prohibited the pupil from affecting light reaching the retina as it normally does.

An on-line GE-225 digital computer with integral analog-to-digital and digital-to-analog conversion equipment was used in the experimental phase of the study. The on-line computer was used to generate the Gaussian noise stimulus and to input the corresponding response. Stimulus and response were punched on cards in a highly compressed binary format for further data processing. The necessary high-order correlation and averaging programs were written in Fortran and run on IBM 7094 at the Massachusetts Institute of Technology Computation Center. Computation time for evaluation of the first and second kernels seen in Figure 15 was approximately ten minutes.

The on-line computer was also used in the double pulse experiment to generate the required stimuli in a random

order to minimize long term trends and to average the corresponding responses. At the termination of the experiment, the average response data was punched on cards. Another relatively simple program performed the necessary algebraic manipulations on the data and plotted out the second order kernel.

EXPERIMENTAL RESULTS

Noise Excitation

Figure 13 illustrates typical input-output data for pupil system's response to random light excitation. From sinusoidal experiments we have seen that the pupil system has negligible response beyond 4 cps. As a consequence, the noise bandwidth was made about 10 cps. The rectification-like nonlinear behavior is clearly evident by noting the sharp difference between the steady state pupil area before and during excitation. The computer was also programmed in such a way as to be able to output the same pseudo-random stimulus many times in order to observe the effect of noise unrelated to the excitation. Input-output data for two identical pseudo-random stimuli functions is seen in Figure 14. Finite data length and random pupil variation unrelated to the input were the main sources of error. In the taking of experimental data, the subject is instructed not to blink for periods up to one minute inasmuch as such a strain on the subject often introduces unwanted drift as the run proceeds. It was found very useful to subtract from the data the best—in the least square sense—second order equation as an attempt to cope with this problem. If this is not done, one may obtain experimental auto- and cross-correlations which have large variation from run to run.

Figure 15 shows the first and second order kernels which are basically of opposite sign. The shape of the first order kernel and that of the main diagonal slice of the second closely resemble a pulse response. The width of the second order kernel off the main diagonal (see right bottom of Figure 15 for cross-section of h_2) is only about one-half second indicating that there is no second order nonlinear interaction longer than this time.

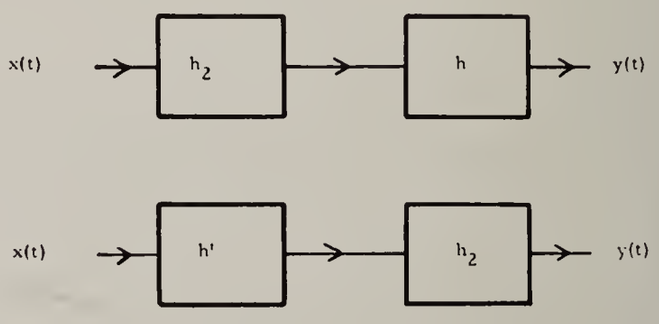


Fig. 11.—Permutations of a second order kernel and a linear system.

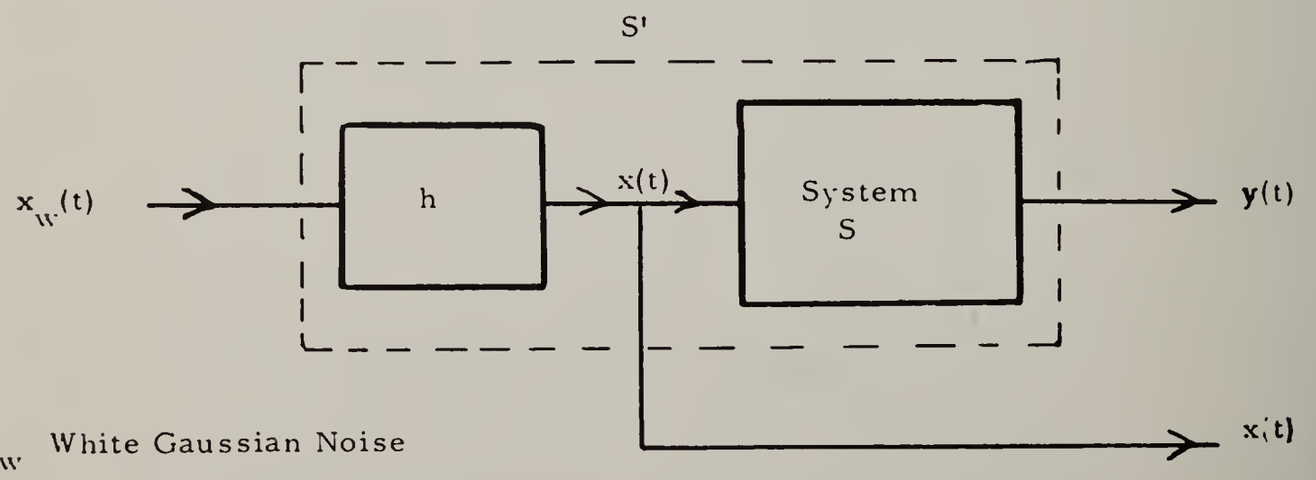


Fig. 12.—Measurement of high order kernels with non-white Gaussian noise.

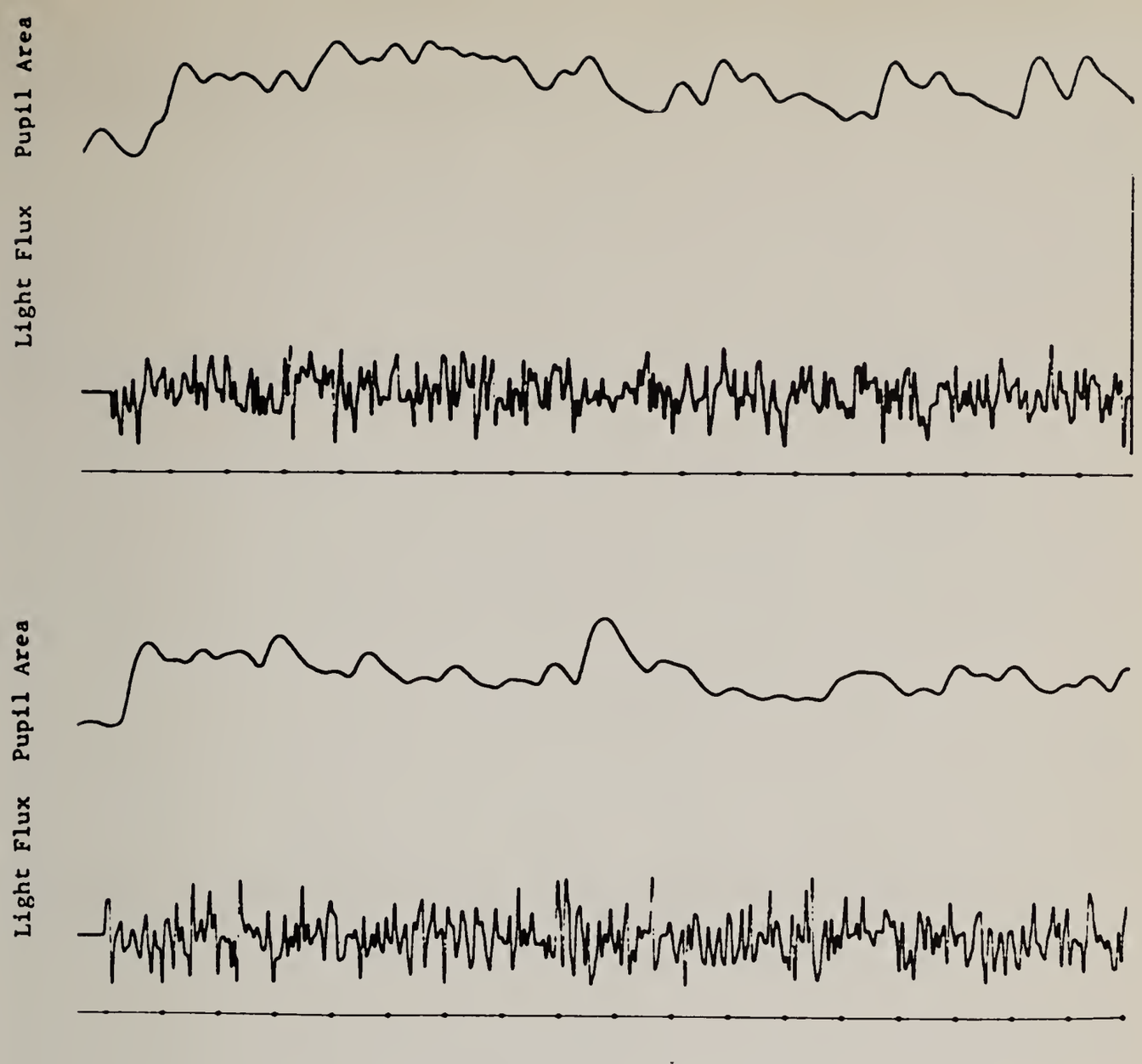


Fig. 13.—Effect of asymmetry on pupil response to random excitation.

Double Pulse Excitation

Stimulus response records for the double pulse experiment are seen in Figure 16.[12] Basically, the relatively noise-free nature of the data is due to two factors: the pulse experiments were performed at relatively low light with the subject fixating at optical infinity thereby eliminating the large amount of noise related to high levels of illumination and near fixation, and extensive computational averaging of the data.

If one examines the data closely it would be observed that the latent period is the same for the second as for the first pulse response. This implies that the higher order kernels all have the same inherent time delay which would seem to indicate that the time delay mechanism is not intimately connected with the nonlinear interaction process.

Figure 17 shows the computed second order kernel, under the assumption that the system can be completely described by just the first two terms in a Volterra expansion. That the shapes of the slices shown in Figure 17 closely resemble the elementary pupil pulse responses again emphasizes the importance of nonlinear interaction occurring before the basic time shaping mechanism occurs in the system. Note also that the spread off the main diagonal is appreciably greater in the double pulse experiment than in the noise experiments.

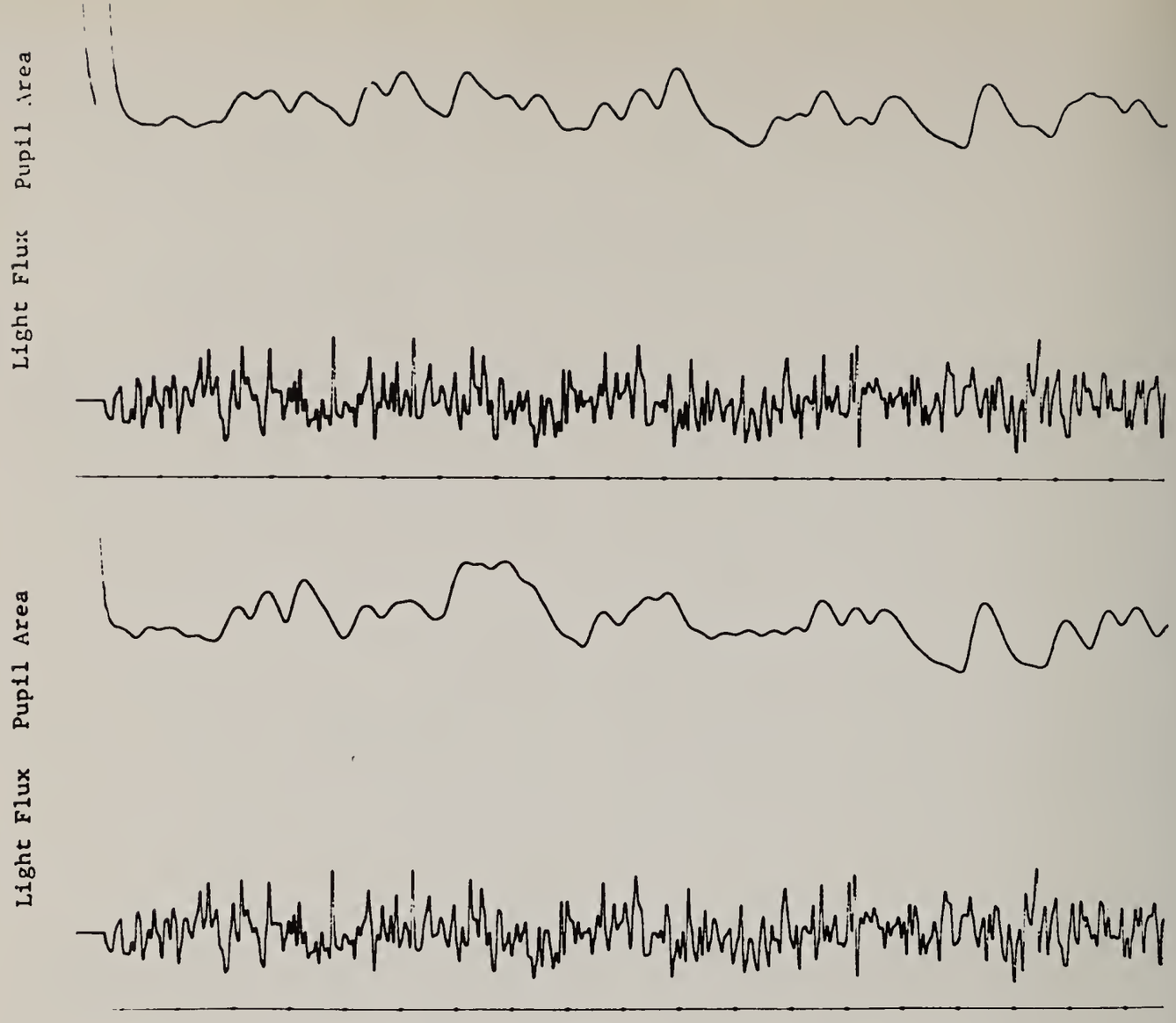


Fig. 14.—Pupil response for two identical pseudo-random stimuli functions.

DISCUSSION

The difference in spread of the two kernels found is surprising. One can hypothesize that the relatively narrow width of the random kernel is due to the pupil being at a small average area because other experiments indicate a larger bandwidth of the pupil system when the pupil is small. Another possibility is that the continued excitation put the neurological portion of the system into a state where nonlinear interactions are greatly reduced.

The basic sign difference between the first and second order kernels represents the scale compression nonlinearity mentioned earlier. This is analogous to the first two nonconstant terms of a Taylor series expansion for a logarithmic type curve having opposite signs.

For some values of (τ_1,τ_2) h_2 obtained by random stimulation is of the same sign as the first order kernel. One might therefore conclude that there exists some nonlinear interaction whose effect is to enhance or facilitate the response at a particular time due to the stimulus some time before. This is in contradiction to the double pulse experiment described here. It would indeed be interesting to see the results of experiments suitably designed so as to emphasize this phenomena if it exists. A more probable, though less provoking, interpretation is that the negative going portion of h_2 will have no effect on the output if we were to carry out the function expansion further.

In attempting to characterize a nonlinear system such as the pupil light reflex, it is good to have as many alternative methods of investigation as possible.

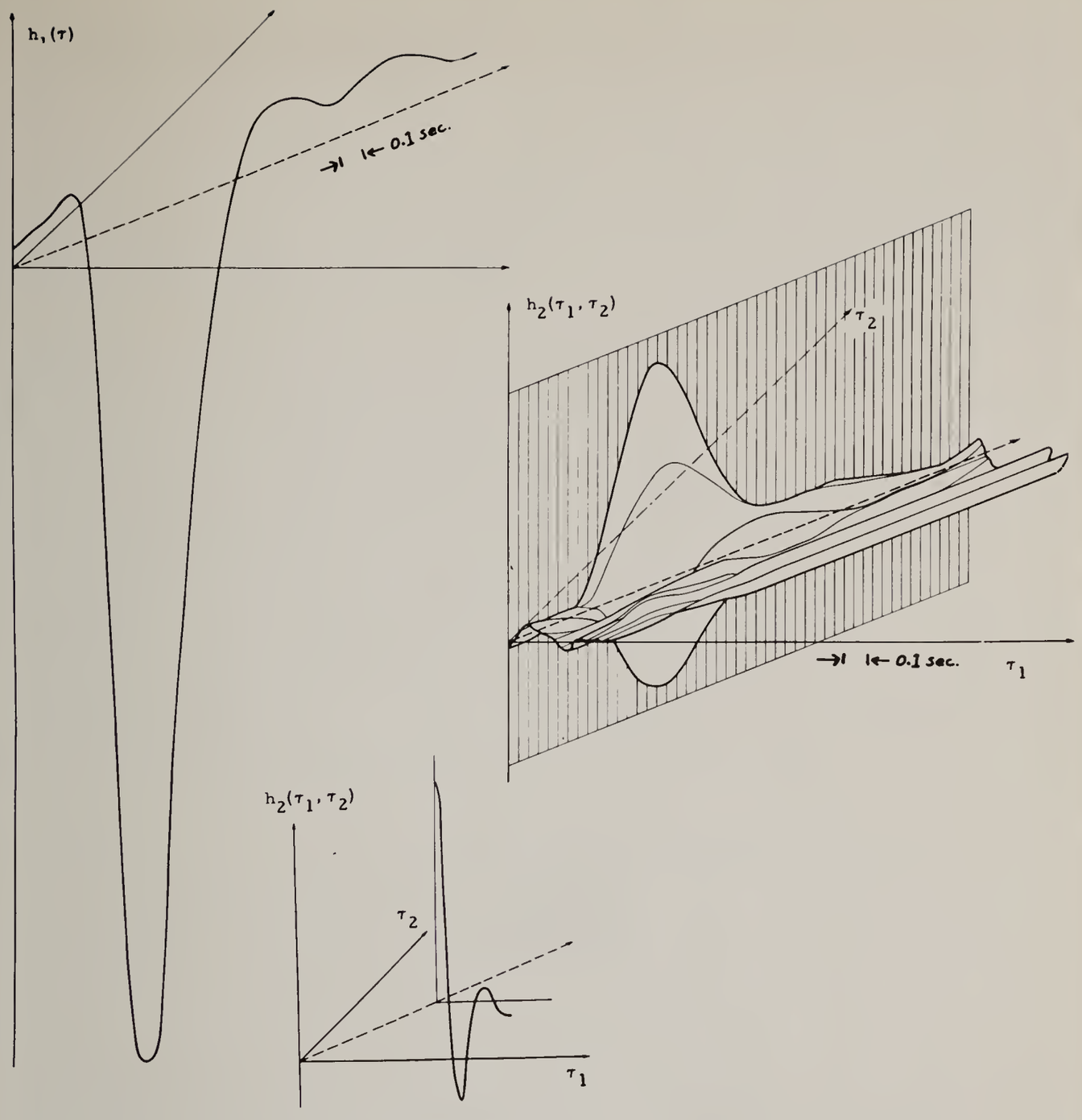


Fig. 15. Wiener kernels $h_1(\tau)$, $h_2(\tau_1,\tau_2)$, and cross-section of h_2.

Unfortunately, it is often difficult to quantitatively relate the results of the different methods described here. The first two methods of characterization have been used with considerable success in describing biological systems: sinusoidal analysis is a very familiar approach in linear system analysis and people have developed a good feeling for it and its application; heuristic modeling guides one, hopefully, to the threshold of understanding or—which is even more important—into asking questions one would never have thought of without the model.

The functional analysis approach to the human pupil light reflex was attempted for two reasons. First, we wished to develop a canonical representation of the system which would make evident in a mathematical manner certain characteristic nonlinearities of the system. Secondly, we wanted to explore the usefulness of the Wiener-Lee theory of nonlinear systems on a real problem of characterization where a comparison with other methods could be made. The main application of the theory to date has been to solve problems which would be less elegantly solved by other techniques. □

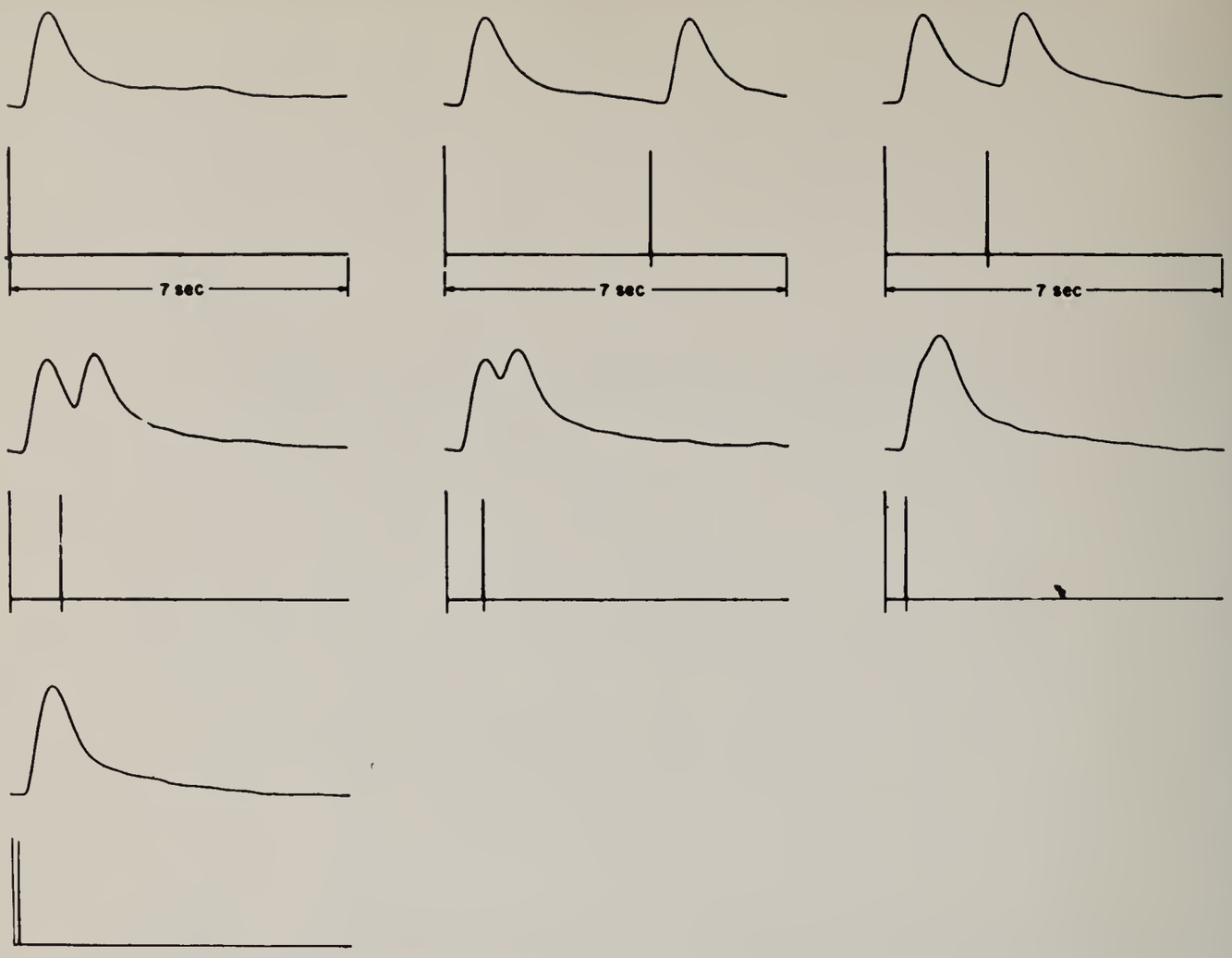


Fig. 16.—Double pulse light stimulation of the human pupil system.

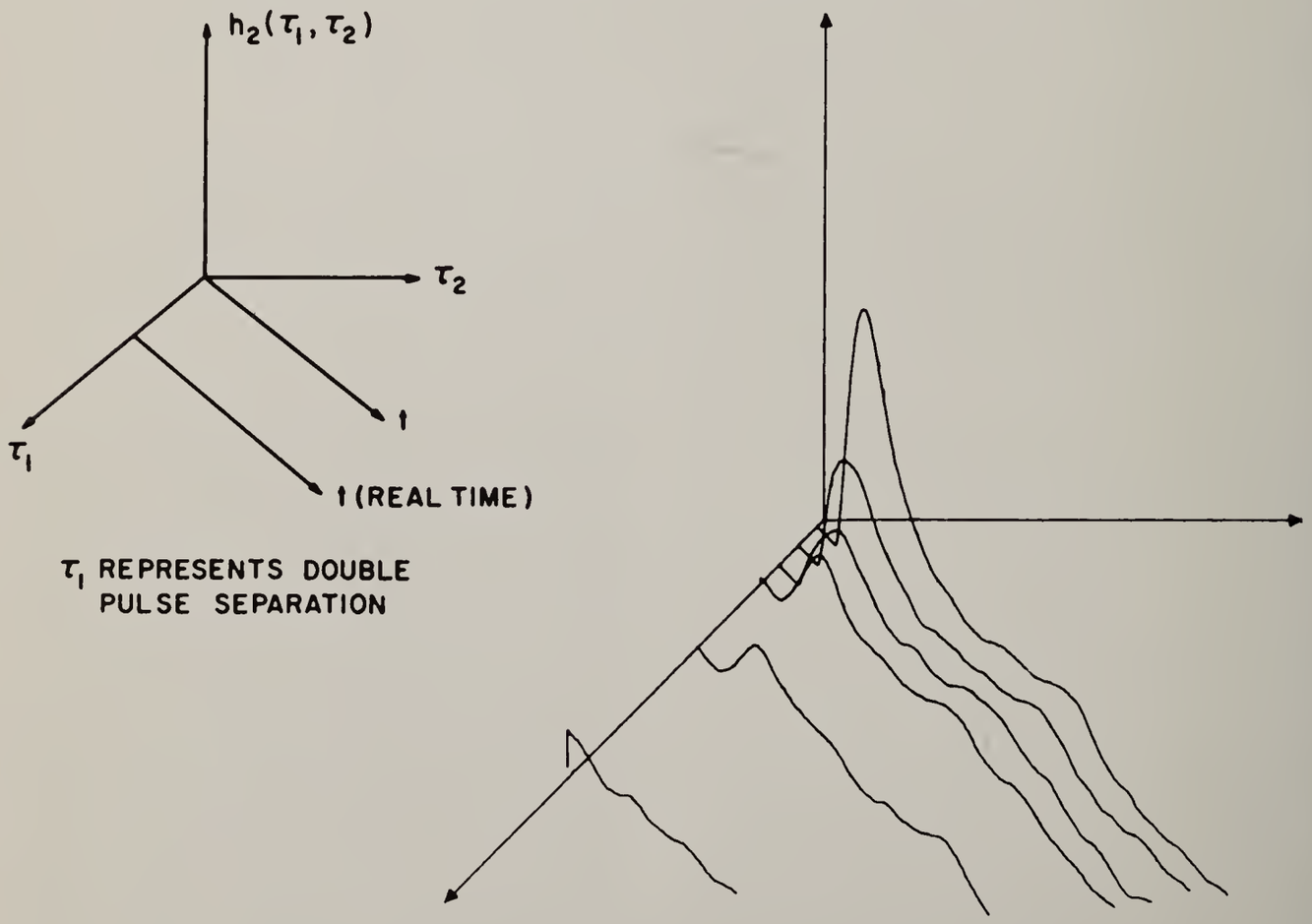


Fig. 17.—Second order Volterra kernel as derived from double pulse experiment.

SUMMARY

Three general approaches to nonlinear input-output systems are contrasted.

1. Describing function based mainly on sinusoidal excitation functions.
2. Heuristic experimental analysis coupled with model building based on intuitive guesses as to component connections, component characteristics, and efficient particular transient inputs.
3. Wiener G-functional expansions based upon stochastic driving functions.

The mathematical methods for experimental measurement of the kernels of a system are described for random signals and multi-pulse inputs.

The effect of topological arrangement of component boxes and of input noise bandwidth on the methods above are discussed. Apparatus and experimental design using an on-line digital computer is briefly described.

The experimental results are separately displayed for random noise and multi-pulse excitation functions.

The first (h_1) and second (h_2) order kernels are of opposite sign and thus represent the first terms of a saturation nonlinearity. (h_1) and the main diagonal slide of (h_2) resemble the pupil pulse response and thus suggest that the nonlinear interaction occurs before the basic quasi-linear time shaping mechanism. The width of (h_2) off the main diagonal is less than one half second indicating that there is no second order nonlinear interaction longer than this time. Similarly the time delay mechanism is shown to be independent of the nonlinear interaction.

The differences noted between the kernels obtained from the random and multi-pulse experiments include greater (h_2) width off the main diagonal in pulse experiments and (h_2) valleys only in the noise experiments. □

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THE EDITOR'S PAGE

"Learning teaches how to carry things in suspense without prejudice till you resolve."

FRANCIS BACON

Since the beginning of the surgical residency program of the Presbyterian-St. Luke's Hospital, there has been strong emphasis on basic surgical research as an integral part of residency training. This emphasis carries forward and builds upon the heritage of both hospitals in their earlier years.

The impetus for the papers here presented is in large measure given by those residents in the program who have worked very enthusiastically and very hard upon a series of experimental studies loosely interrelated in the general field of shock.

Some of the papers took their initial form in a shock seminar in June of 1965. This forum was requested by the resident participants in order to provide open dissemination of ideas between those who were leaving the year of major laboratory emphasis and those who were about to enter this year.

All of the contributors are continuing in surgical research. Their activity significantly illustrates the benefits to the educated sugeon which may accrue from application to research: an open-mindedness, a willingness to look long and hard for new answers (in fact, for new questions), and a way to escape from the lethal tendency toward a stifling dogmatism.

It is our cherished belief that such pursuit must result in great progress in patient care. To such a goal this issue is dedicated.

HAROLD A. PAUL, M.D.
Special Editor
Symposium on "Shock"

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Renal Cysts in Children

Mammography and the Surgeon

Histologic Changes in the Trachea Following Tracheostomy

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SQUAMOUS CELL CARCINOMA DEVELOPING IN THE CHRONIC DRAINING SINUSES OF OSTEOMYELITIS*

William F. Hejna, M.D.[1]

INTRODUCTION

The present study is a report of 19 squamous cell carcinomas which developed in sinuses of chronic draining osteomyelitis. The purpose of the review is to increase awareness of this lesion by adding a significant series to the literature, and in doing so, to emphasize the pathology and prognosis. Fourteen male and five female patients at the University of Illinois and Presbyterian-St. Luke's Hospital were found to have the lesion under discussion during the period from 1945 to 1963. Their ages ranged from 34 to 80 with an average of 55.4 years. The pre-existing chronic infection was present an average of 24.8 years, the shortest 2.5 years and the longest 65 years. In twelve instances a change in the characteristics of the lesion was noted by the patient an average of ten months prior to the time of diagnosis. Table I tabulates the case material on the basis of definitive treatment carried out and the average follow up period for each of these groups. It may be noted that sixteen of the nineteen cases were in the lower extremity. In Table II the cases are similarly grouped and prior treatment, local and groin node biopsies, and metastases are indicated. The average time from diagnosis to death among the five who did not survive was eight months, and the average follow up of those alive was five years to eleven months.

The symptomatology in these cases included an increase in pain and the amount of malodorous drainage. Further, the edges of the sinus or the ulcer became piled up and progressed in most instances to a fungating mass with a gray-green exudative coating. Histologically, the typical changes of squamous cell carcinoma of skin were seen. Usually, well differentiated carcinoma with moderate disorganization of architecture and many keratin pearls characterized these tumors. However, occasionally anaplastic, vacuolated cells with numerous mitotic figures could be seen invading bone.

Roentgenographically, it is difficult to differentiate the neoplastic from the infectious process when such a combination exists. Suspicion, however, must be aroused when an increase in bone destruction is noted. Typical cases are shown in Figures 1, 2, and 3.

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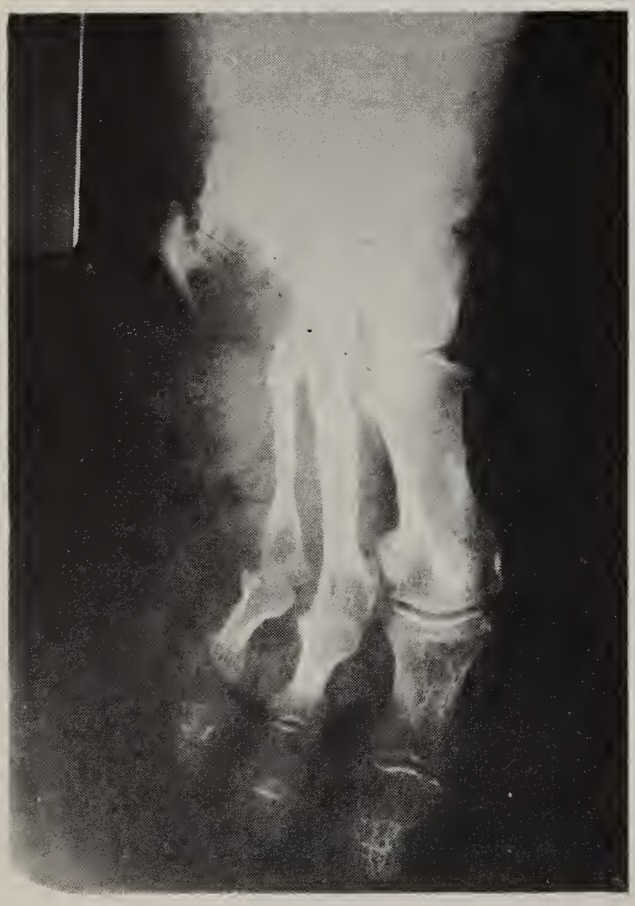
TABLE I

Treatment	Case	Age/ Race/ Sex	Site	Duration of Infection	Etiology	Course	Follow Up	Average Follow-Up
LOCAL RESECTION	1	44 W M	os calcis	27 yrs.	open fracture	Alive and Well	7 yrs.	
	2	45 W M	trochanter	20 yrs.	paraplegia	Dead—Pulm. Embolus	5 mo.	4 yrs. 2 mo.
	3	55 W F	femur	38 yrs.	hematogenous	Alive and Well	5 yrs.	
DIGIT AMPUTATION	4	77 W F	thumb	22 yrs.	split nail	Alive and Well	2 yrs.	
	5	80 N F	toe	5 yrs.	open fracture	Dead—Lung Metast.	2 yrs.	1 yr. 8 mo.
	6	55 W M	phalanx	2.5 yrs.	hematogenous	Alive and Well	1 yr.	
BELOW KNEE AMPUTATION	7	48 W M	tibia	34 yrs.	open fracture	Alive and Well	10 yrs.	
	8	80 W M	foot	5 yrs.	laceration	Alive and Well	14 yrs.	
	9	73 W M	tibia	40 yrs.	hematogenous	Alive and Well	1 yr.	
	10	54 W M	os calcis	29 yrs.	open fracture	Dead—Pneumonia	4 mo.	4 yrs. 7 mo.
	11	51 W M	foot	22 yrs.	nail puncture	Alive and Well	1 yr.	
	12	80 W M	tibia	65 yrs.	hematogenous	Alive and Well	1 yr.	
ABOVE KNEE AMPUTATION	13	69 W F	tibia	53 yrs.	hematogenous	Alive and Well	2 yrs.	
	14	27 W M	tibia	15.5 yrs.	open fracture	Alive and Well	8 yrs.	
	15	37 W M	femur	12 yrs.	surg. infection	Alive and Well	2 yrs.	5 yrs. 9 mo.
	16	58 W M	foot	27 yrs.	crush injury	Alive and Well	16 yrs.	
	17	35 W M	tibia	20 yrs.	hematogenous	Alive and Well	1 yr.	
HIP DISARTICULATION	18	51 W M	femur	36 yrs.	hematogenous	Dead—Bowel Obstruction	1 mo.	
NO SURGERY	19	34 W F	Sacrum	?	decubitus	Dead—pneumonia	6 mo.	

TABLE II

	Case	Prior Treatment	Local Biopsy	Groin Node Biopsy	Radical Groin Dissection	Lung Metastases	Survival
LOCAL RESECTION	1	Debridement	Negative	Negative	0	0	Alive
	2	Debridement	0	0	Positive	0	Dead
	3	Debridement 8X	0	0	0	0	Alive
DIGIT AMPUTATION	4	3 local exc.	0	0	0	0	Alive
	5	0	0	0	0	Probable	Dead
	6	I & D	0	0	0	0	Alive
BELOW KNEE AMPUTATION	7	0	Negative	Negative	0	0	Alive
	8	0	Negative	Negative 2X	0	0	Alive
	9	0	0	0	0	0	Alive
	10	0	0	Negative	Positive	0	Dead
	11	I & D	0	0	0	0	Alive
	12	Debridement 2X	0	0	0	0	Alive
ABOVE KNEE AMPUTATION	13	0	0	0	0	0	Alive
	14	X-Ray	0	0	Negative	0	Alive
	15	Sequestrectomy	0	0	0	0	Alive
	16	0	Negative 3X	Negative	Negative	Proven	Alive
	17	0	Positive	Negative	0	0	Alive
HIP DISARTICULATION	18	0	0	0	Positive Autopsy	0	Dead
NO SURGERY	19	0	Positive	0	0	0	Dead

a.



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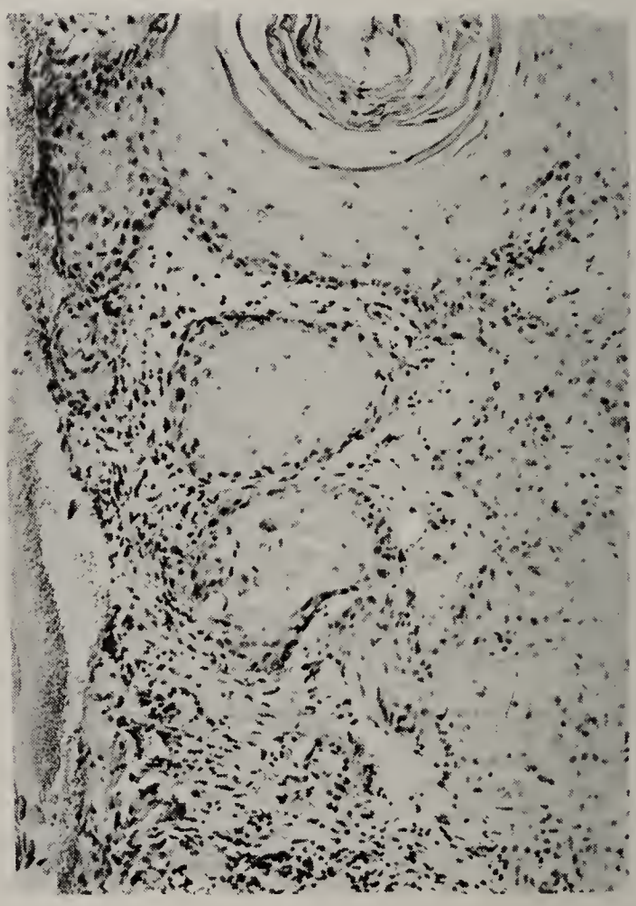


c.

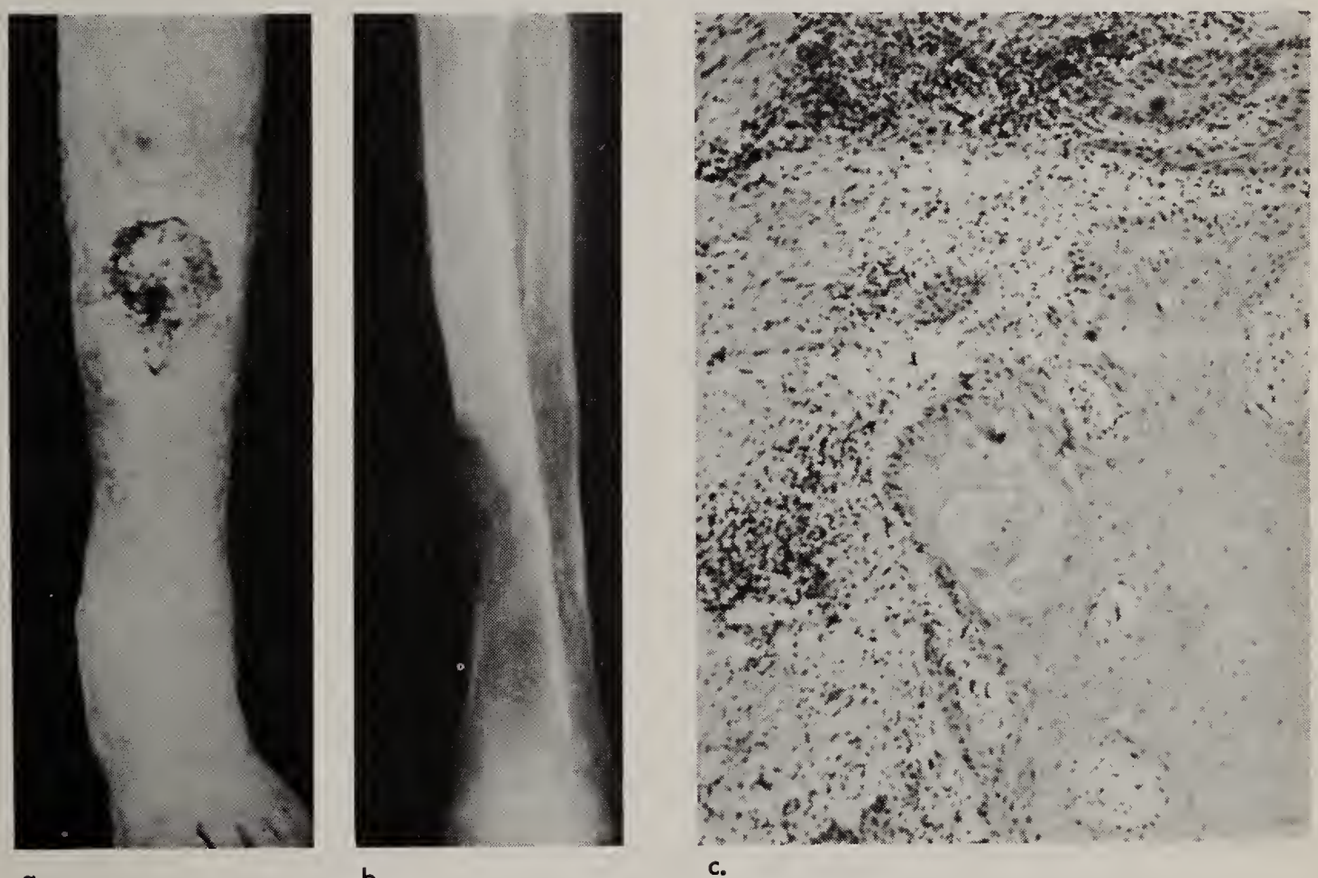
Fig. 1.—a, b, and c, Case #8 (See Tables)

FOLLOW UP DATA

The average period of follow up was 5.1 years; the longest sixteen years and the shortest eleven months. This excludes one case which was lost to follow up and four who died within six months of surgery. Prior to making the diagnosis of epidermoid carcinoma, nine patients had a total of twenty-three operative procedures of various types for osteomyelitis.

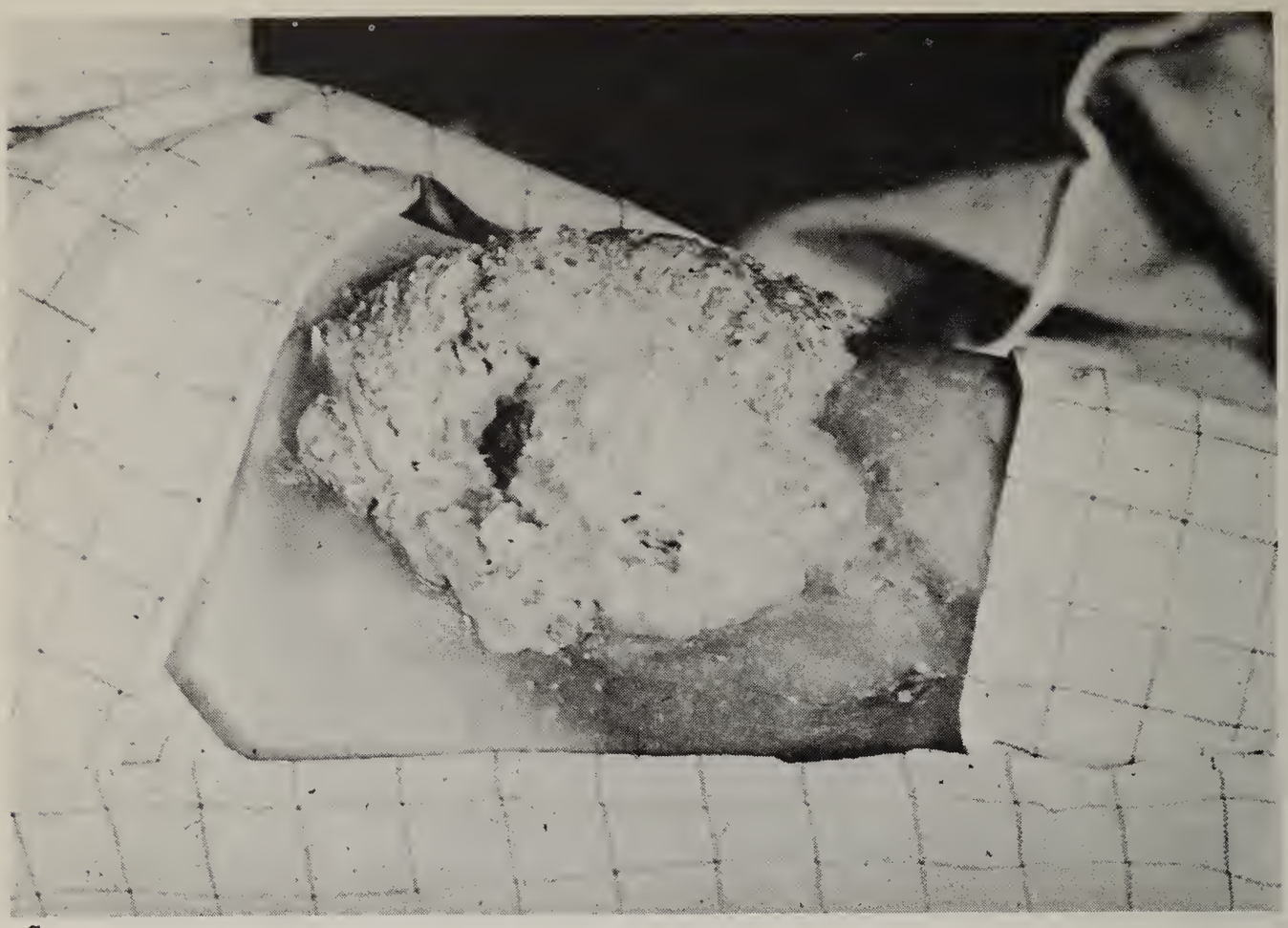
The definitive treatment consisted of local resection of the draining sinus and tumor in three cases, amputation in fifteen cases, and no surgery in one case. Among the three local resections, one was in a foot and unrecognized prior to surgery. This patient is alive without metastases after seven years. A second was done in the trochanteric region in a patient who also had a positive groin node dissection and died five months post-operatively of a pulmonary embolism (Case 2). The third was an unexpected finding when saucerization was performed on a femur (Case 3). Above knee amputation was carried out on this patient five years later for persistent drainage, and no carcinoma could be found in the amputated specimen.

Among the fifteen patients who had an amputation, one died one month post-operatively of bowel obstruction and was proven to have abdominal node metastases at autopsy (Case 18). One patient with a below knee amputation also had a positive groin node dissection and died four months post-operatively with bronchopneumonia (Case 13). One patient with x-ray findings suggestive of pulmonary metastases died at home and an autopsy could not be done (Case 5). Twelve of these fifteen patients are alive including one who later had a pneumonectomy for a metastasis (Case 16). Three other of these fifteen patients had radical groin and iliac node dissections and no tumor was found. One patient (Case 19), died of severe inanition and pneumonia six months after a biopsy diagnosis was made. No definitive treatment had been carried out.



a. b. c.

Fig. 2.—a, b, and c, Case #13 (See Tables)



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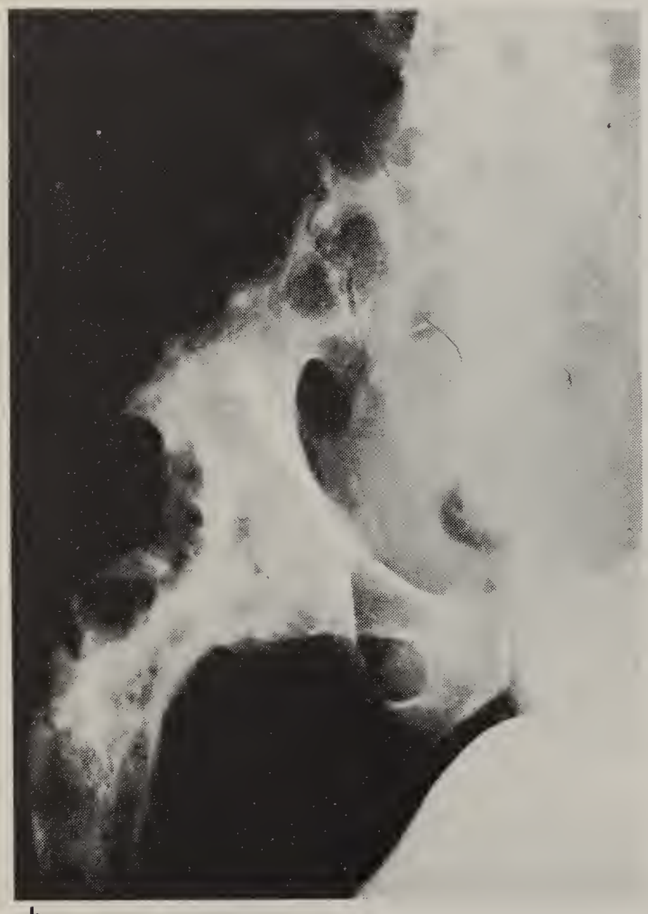

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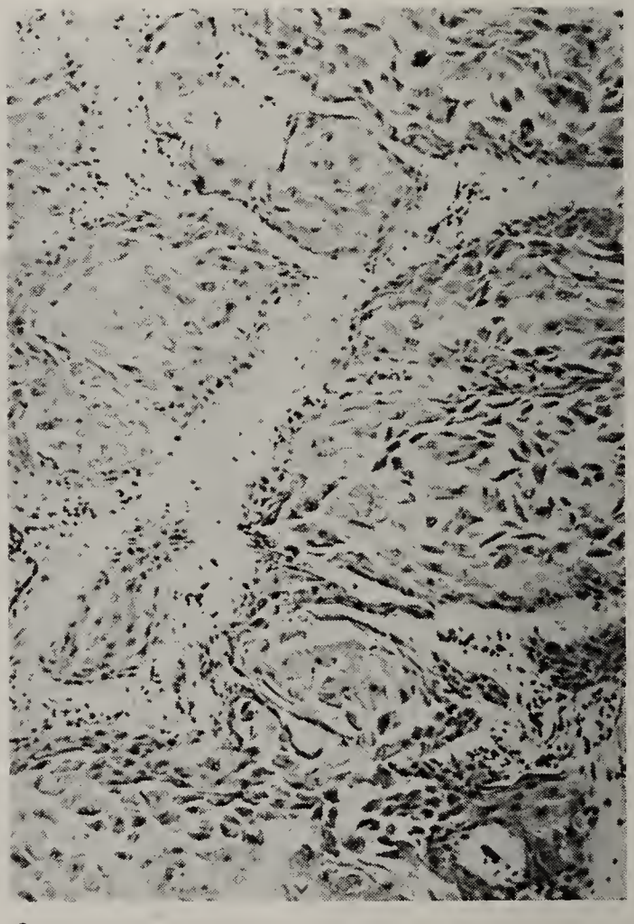

c.

Fig. 3.—a, b, and c, Case #18 (See Tables)

DISCUSSION

In 1828 Marjolin[7] first recognized that the squamous cells bordering or lining chronically infected areas may develop malignant characteristics. Reports of this condition then remained scanty for about 100 years when Benedict[1] reviewed the subject in 1931 and added 12 cases to 39 he found in the literature. He reported no deaths and stated that the prognosis was good. Henderson and Swart[5] however, reported that one case in their series of 5 had a groin node metastasis and reports by Berestan and Ney[2] and McAnally and Dockerty[8] also included nodal metastasis in 1941 and 1949 respectively. The first pulmonary metastasis was reported by Hellner[4] in 1936. A further comprehensive review was then made by Sedlin and Fleming in June 1963 and 12 additional cases were reported. Twenty-two regional or visceral metastases occurred among the 102 patients discussed by these authors, and the survival rate was low. This evidence offered a pessimistic prognosis contrary to the writing of other authors.[1,3,6]

Nodal biopsy and groin dissection deserve further comment. It should be noted that inguinal node biopsy was done seven times and was negative in all instances. Further, of the four radical inguinal and iliac node dissections performed, two had positive nodes and both of these patients died on the same hospital admission. Tumor cells were found in abdominal lymph nodes at postmortem in one additional case, (Case 18). The inguinal lymph nodes are enlarged and firm in most instances due to the presence of chronic infection, therefore, surgical attack to this area should be carried out only after extremely conscientious evaluation.

Local biopsy was carried out eight times and was negative for carcinoma cells six times. This is probably due to a misleading exudative process and location of the tumor deep within the sinus. These negative biopsies point up the importance of clinical evaluation and the difficulty in recognizing tumor tissue grossly. It is felt that estimation of what comprises an adequate local resection is difficult when bone has been invaded. □

CONCLUSION

The author therefore, supports the view that these tumors can be aggressive in spite of their well differentiated histologic characteristics, and that amputation when feasible, is the treatment of choice. □

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□

RENAL CYSTS IN CHILDREN

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INTRODUCTION

Cystic disease of the kidney, although by no means a common condition, has historically attracted widespread interest among physicians. Known to exist for several centuries, even today the diagnostic and therapeutic considerations of renal cyst continue to stimulate the interest of physicians of many disciplines. The purpose of this presentation is to review the clinical features of the various cystic disorders in childhood. Unfortunately, the term *infantile polycystic kidney* with its ensuing grave prognostic outlook is often used to designate all renal cystic lesions in the pediatric age group, although several forms of cyst occur in children which carry a favorable outlook.

PATHOGENESIS

Until recently, interest in pathogenesis has been almost entirely directed towards explaining polycystic kidney disease Because of the dual embryologic origin of the permanent kidney, namely the outgrowth of the ureteric bud from the Wolffian duct, which becomes capped by condensation of mesenchyma called the metanephric blastema, failure of union of these two parts was postulated to result in the formation of polycystic kidney.[1] This theory held that a lack of the normal joining of these two separate tubular systems lead to cyst formation since glomerular filtrate failed to be carried away. McKenna and Kampmeier[2] later demonstrated that in the sprouting, branching, and re-branching through successive generations of the ureteric bud that some of the early order of buds become separated from the parent lumen and persist for a time as cystic structures, and then finally degenerate. Polycystic disease was thought to develop when these vestigial cystic structures failed to disappear with subsequent cystic formation within the permanent kidney. Many other theories and modifications of these two original basic embryologic explanations have been suggested but since polycystic disease is not susceptible to experimental reproduction, all contain a considerable element of speculation.

Two recent studies, utilizing microdissection techniques in the stillborn kidney, have defined, in a more precise way, the nature and origin of renal cysts. Bialestock[3] in Australia, by dissecting various types of renal cysts, was able to determine different types of embryological defects. In unilateral multicystic kidney the nephron dissected out intact until it suddenly ended blindly at the level of the distal convoluted tubule. No subsequent tubular connection could be demonstrated. Polycystic kidney, on the other hand, was shown to contain an entirely intact nephron, although in many instances the nephron

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was of large size, designated as a giant type. Several peritubular cystic structures were also demonstrated in polycystic disease. By utilizing microdissection studies, Osathanondh and Potter[4] have been able to divide kidneys containing cysts into four different types. Type 1 is characterized by hyperplasia of the interstitial portions of the collecting tubules, a bilateral condition usually fatal in early life. Type 2 is characterized by abnormal ampullae, which apparently are responsible for lack of nephron induction, permanent cessation of collecting tubule branching, and cystic dilatation of terminal portions, involving part or all of one or both kidneys. Type 3 is characterized by abnormality of both the interstitial and ampullary portions of the collecting tubules, branching of ampullae and induction of nephrons being abnormal, with any part of the nephron or collecting tubule becoming enlarged or cystic. These abnormal units are interspersed between normal areas of renal parenchyma. Type 4 is characterized by mild irregularity in branching and local enlargement of tubules caused by lower urinary tract obstruction with excessive back pressure apparently injuring the very young ampullae.

Fig. 1—Unilateral multicystic kidney. Surgical specimen from 4 day old child. Atretic ureter is represented only by a fibrous band. Reniform contour of kidney is lost.

Fig. 2.—Simple serous cyst, exposed at surgery. Two thin walled cysts are noted, each as large as the kidney.

Unilateral Multicystic Kidney

The striking feature of this lesion is the replacement of one entire kidney by irregularly lobulated cystic masses varying in size from that of a pea to a hen's egg, which are held together like a bunch of grapes by loose connective tissue. (Fig. 1) The architecture of calyces, pyramids, and cortex is completely lost and microscopically there is no normal parenchyma except for an occasional nubbin of immature glomerulus or tubule. The ureter is commonly atretic at some point in its length and it may be reduced to a minute thread or be altogether absent. The blood supply to the kidney may be variable and in some instances the pedicle is absent. Microscopically the cyst wall is composed of fibrous tissue lining with a single layer of flat epithelial cells. The entity is characteristically confined to one side only, in contrast to congenital plycystic disease of the kidney, which is usually bilateral. In addition, the general reniform contour is retained in polycystic kidney, whereas it is completely lost in multicystic kidney.

Review of the literature discloses an occasional description of this entity often designated differently. Campbell[5] depicts the lesion as being unilateral polycystic kidney. In Gross's *Surgery of Infancy and Childhood*[6] no mention is made of it in the text but two pictures are noted of specimens that would appear to be similar to unilateral multicystic kidney. Schwartz[7] is credited with the first report of a case in 1936; and Spence[8] in 1955 reported four cases and in reviewing the literature found 15 more. In reviewing our experience with unilateral multicystic kidney, we have found 22.

Multicystic kidney usually has been observed in the newborn period when an abdominal mass was found. This mass has been associated with absence of pyelographic visualization of the kidney on the involved side and ureteral atresia of the upper segment when retrograde pyelography was attempted. The opposite kidney characteristically has been free of cystic degeneration, although other non-cystic renal congenital abnormalities, such as ureteropelvic junction obstruction, may be present. The treatment in all but one instance, that of a premature infant, has been nephrectomy.

Unilateral multicystic kidney is more common than is generally appreciated. We have seen six such cases in the past 30 months. Its presence should seriously be considered when an abdominal mass presents in the newborn period. Its differentiation from Wilms's tumor and neuroblastoma should not be difficult since pyelographic visualization usually occurs with these malignancies. Giant hydronephrosis can be associated with

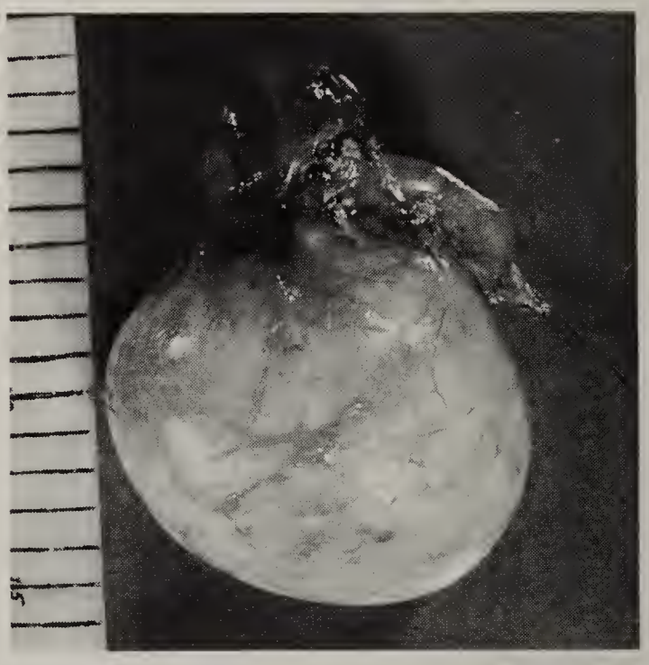

Fig. 3.—A. Multilocular cyst. Surgical specimen of 2 year old child. Massive replacement of major portion of kidney. Cystic character of lesion is not apparent.

Fig. 3.—B. Multilocular cyst. Surgical specimen of 2 year old child. Cut surface reveals cystic character.

non-visualization of the kidney, but retrograde pyelography should clarify the diagnosis.

Simple Serous Cysts

By far the most common cystic disorder of the kidney, simple serous cyst is rarely clinically apparent in childhood. The term, simple serous, rather than solitary, is more accurate since simple cysts are usually multiple, although the disproportionate size that any one cyst can attain may suggest it is the only lesion present. (Fig. 2) Simple serous cyst may attain huge size and are characterized by thin "blue domed" walls which usually grow outward away from the renal substance rather than inwards, thus producing less renal damage than one might expect. Renal infection and an abdominal mass are the presenting features in childhood. The preoperative differentiation from malignancy, utilizing renal arteriography, nephrotomography, and renal scans, have not been employed since the likelihood of tumor presence has usually prompted immediate surgery. Simple serous cysts usually, but not always, occur in the lower pole and can often be simply unroofed surgically leaving the remainder of the kidney undisturbed.

Multilocular Cyst (Cystadenoma)

This interesting cystic malformation is characterized by replacement of a major portion of one kidney by a smooth, solid spherical mass with a thickened capsule. (Fig. 3,A) The cystic character cannot be determined until after the specimen is sectioned, (Fig. 3,B) when the multiloculated character and semi-gelatinous fluid content then become apparent. The uninvolved portion of the kidney and the opposite kidney are usually normal.

Clinically, multilocular cysts present as an abdominal mass in childhood. This mass together with pyleographic distortion of the renal pelvis gives rise to the

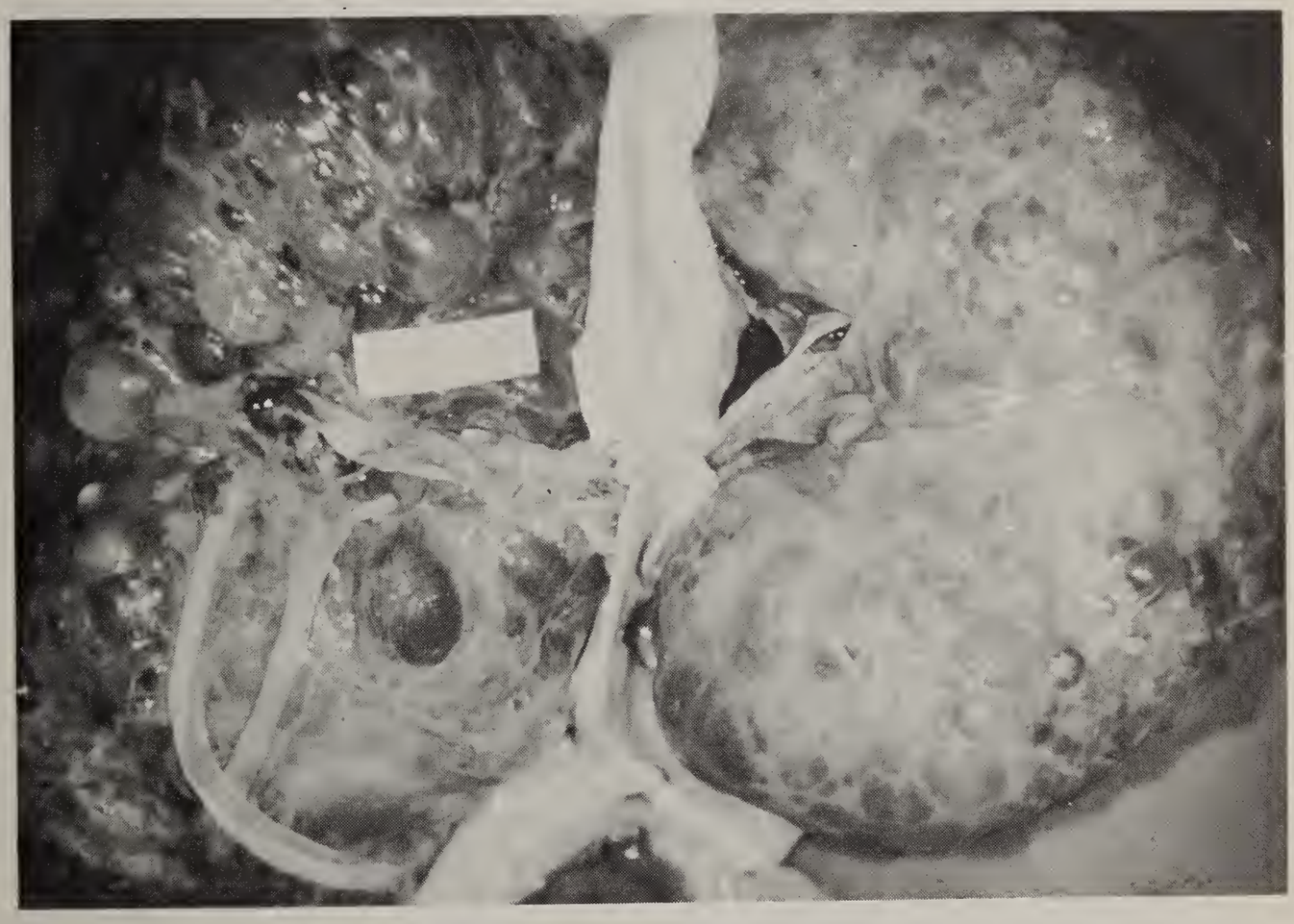

Fig. 4.—Adult form of congenital polycystic kidney. Autopsy specimen of 48 year old man. Bilateral massive enlargement of kidneys is noted. Reniform contour maintained.

suspicion of Wilms's tumor. Nephrectomy is the treatment of choice since the nonmalignant character of the lesion is not certain until after removal of the kidney.

Congenital Polycystic Kidney

The term congenital polycystic kidney defines that renal disorder characterized by diffuse involvement of both kidneys by innumerable cysts on a hereditary basis. This term with its grave prognostic outlook should not be indiscriminately applied to any renal lesion composed of more than one cyst.

Clinically this disease is of two types: the infantile form in which the great majority of afflicted infants are stillborn or die within the first few hours of birth, and the adult form in which the complications of polycystic kidney do not occur until beyond childhood. Pathologically the infantile form of polycystic kidney is characterized by general enlargement of the kidneys, and the cystic nature of the condition is not observed until on section a honeycomb appearance with thousands of minute oval or elongated cysts arranged in radial fashion throughout the parenchyma are observed. The more common adult form (Fig. 4) is characterized by gross distortion of the kidney by cysts of varying size which are irregularly arranged throughout the parenchyma. These cysts gradually enlarge to produce renal insufficiency in adulthood but on occasion produce hematuria, a palpable mass and renal rickets in childhood.[9]

The diagnosis and treatment of this condition are well established.[10] Treatment is concerned mainly with management of the failing kidney and surgery is seldom required. Cystic degeneration of other organs, such as liver, lung, pancreas, ovaries are not uncommon.

Renal Cyst Associated With Other Urinary Tract Anomalies

Other urinary tract anomalies, not of cystic origin, can be associated with various renal cystic malformations. It is not uncommon to observe cystic degeneration associated with hydronephrosis of infancy due to lower urinary tract obstruction such as urethral valves or bladder neck obstruction. Other urinary tract anomalies occasionally associated with cyst formation include renal hypoplasia, renal dysgenesis, hydronephrosis due to ureteropelvic junction obstruction and horseshoe kidney. (Fig.5)

Calyceal Cyst

Cyst formation in relation to a single calyx is occasionally encountered in childhood. Descriptive terms for this condition include hydrocalyx, pyelogenic cyst, and calyceal diverticulum. Calyceal cyst may be seen in otherwise normal pyleograms or in association with renal hypoplasia. Calyceal cysts are seldom responsible for symptoms, although a stone may form in one and be accompanied by recurrent urinary tract infections.

□

SUMMARY

The various forms of renal cystic disorders of childhood are reviewed. All renal cysts in children are not of the congenital polycystic type. Other varieties, particularly unilateral multicystic kidney do occur and usually carry a favorable outlook.

□

Fig. 5.—Renal cyst associated with other urinary tract anomalies. Autopsy specimen of stillborn. Congenital polycystic kidney associated with horseshoe kidney.

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MAMMOGRAPHY AND THE SURGEON

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INTRODUCTION

Carcinoma of the breast is the most prevalent malignant neoplasm in adult American women today. Its incidence is greater than all other carcinomas of the female generative organs, which constitute 70 per cent of the carcinomas of women. The incidence is increasing while that of carcinoma of the cervix and ovary are decreasing. This is true despite all efforts toward early diagnosis and treatment. Although it has been more than fifty years since Halsted described his results of radical surgery for carcinomas of the breast, and although much work has been done toward identifying the etiology and epidemiology of breast cancer, precise knowledge concerning the natural history and truly effective treatment of disease in man is lacking. The treatment of choice in all but the most extensive lesions is still radical surgery. Regardless of opinion on biologic determinism, early surgery in this lesion is still felt to be the best if not the only method of treatment, which can afford the patient a better than 50 per cent chance of a five year survival.

Where then, does mammography play its role in the management of carcinoma of the breast? It is an attempt to assist in the early or pre-biopsy diagnosis of breast disease. That difficulty is encountered in the diagnosis of breast disease seen in the many other ancillary methods preceding mammography. Transillumination, injection of contrast material into the ducts, and injection of air into the retromammary space have all been tried without much success. Mammography, as it is practiced today, does not involve intraductal injection of contrast media or air into the breast. It is essentially soft tissue radiography of the breast using special techniques, which involve low kilovoltage and high milliamperage, needed to properly portray breast architecture on fine grain industrial film. This method, first described by Leborgne[1] and later popularized by Egan,[2] is essential if one is to record the details of malignant lesions and the very small calcifications which are present in at least one-third of malignant breast neoplasms. These calcifications are pathognomonic of carcinoma of the breast, and oftentimes on the films they are the only positive findings noted. Their presence, when physical findings are confusing, or perhaps even absent, encourages immediate biopsy and, therefore, earlier surgery.

The radiographic appearance of most benign and malignant lesions has now been adequately described.[3] A typical carcinoma and two of the most common benign lesions are shown in Figures 1, 2, and 3.

There are four major clinical situations in which mammography is helpful:

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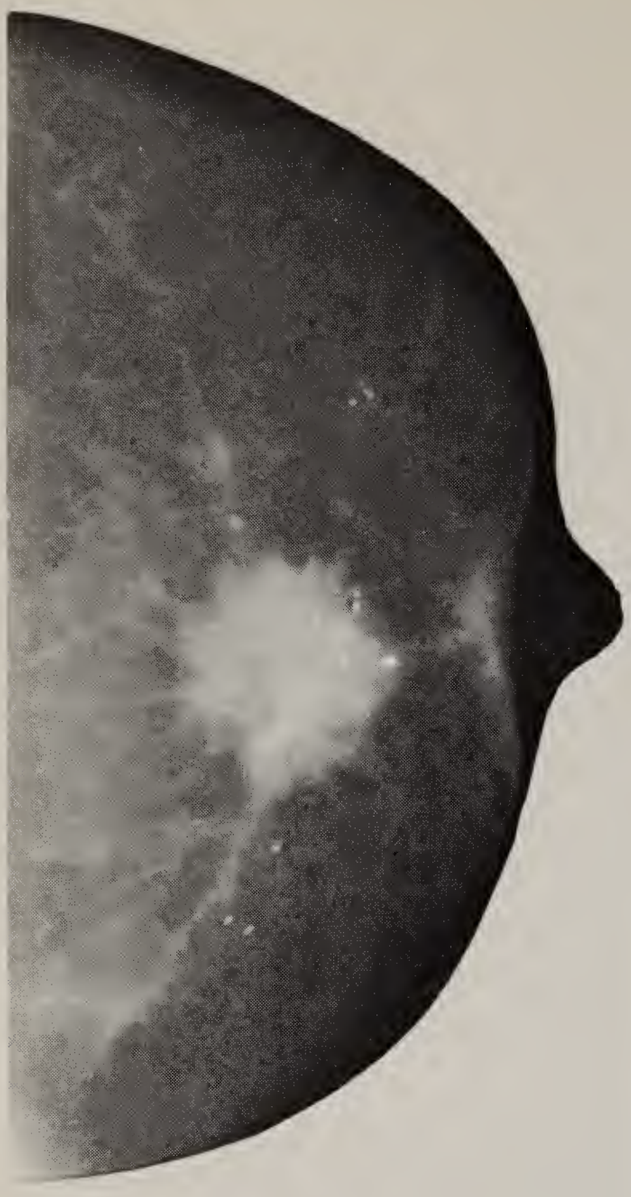

Fig. 1.—Typical malignant neoplasm showing dense mass with markedly irregular and spiculated borders. There is some retraction of the nipple. The appearance is classically that of a scirrhous carcinoma of the breast. (Egan, R. L.: Mammography, Springfield, Charles C. Thomas.)

1. Cases in which there are no obvious clinical masses present. Patients presenting vague breast complaints, such as, "slight fullness" or "slight thickening" or even an area of tenderness, are common. Often the examining surgeon finds no mass, or his palpatory findings are confusing even when present. Mammography can demonstrate that the breast is quite normal, and that the surgeon can reassure his patient that nothing more need be done at this time. He may suggest additional check-ups at appropriate intervals. If a suspicious lesion is seen, then biopsy of the area can be carried out with the possibility that a preclinical malignancy may be discovered.

In patients who have had previous mastectomy for carcinoma of the breast, the overall incidence of another primary lesion in the second breast is in the range of 7½ per cent to 10 per cent.[4] Patients with multiple cancers of the first breast also have a higher incidence of primary carcinoma in the remaining breast.

This is also felt to be true in those who have a strong family history of breast carcinoma. Unfortunately, the diagnosis

Fig. 2.—Solitary cyst with fibrocystic disease. Note the smooth borders and displacement of the fat and trabeculae by the lesion. Note its density which is approximately that of the remainder of the breast. Notice that the immediately surrounding breast architecture is undisturbed. (Egan, R. L.: Mammography, Springfield, Charles C. Thomas.)

of cancer of the remaining breast is not necessarily made at an early stage, although these patients usually have regular check-ups. Robbins and Berg[5] have found that in their series of ninety-four bilateral breast carcinomas, 66 per cent of the second lesions were not considered early when removed. For this reason, a routine mammographic study may detect small lesions before they are clinically evident (Figure 4).

2. The second situation is that of the debatable lesion. These lesions are debatable, not because of their presence, but because of doubt as to their true nature. It is in these cases that mammography can be helpful in deciding whether to biopsy, and, what is probably more important, where to biopsy (Figure 5).

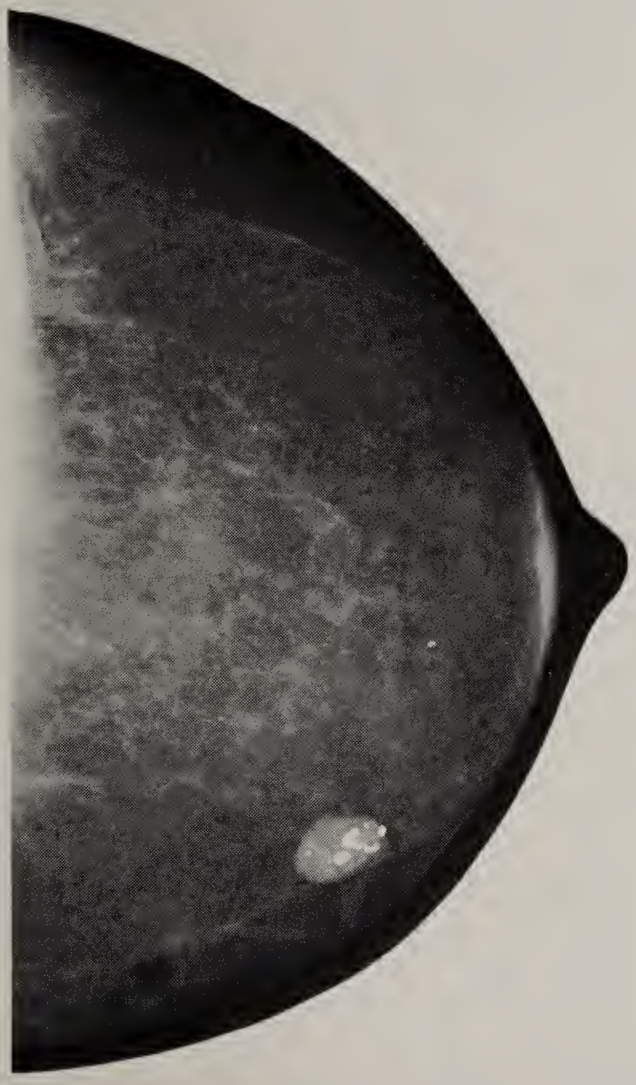

Fig. 3.—Small fibroadenoma showing bosselated or lobulated borders, increased density, and typical coarse calcifications of this lesion. (Egan, R. L.: Mammography, Springfield, Charles C. Thomas.)

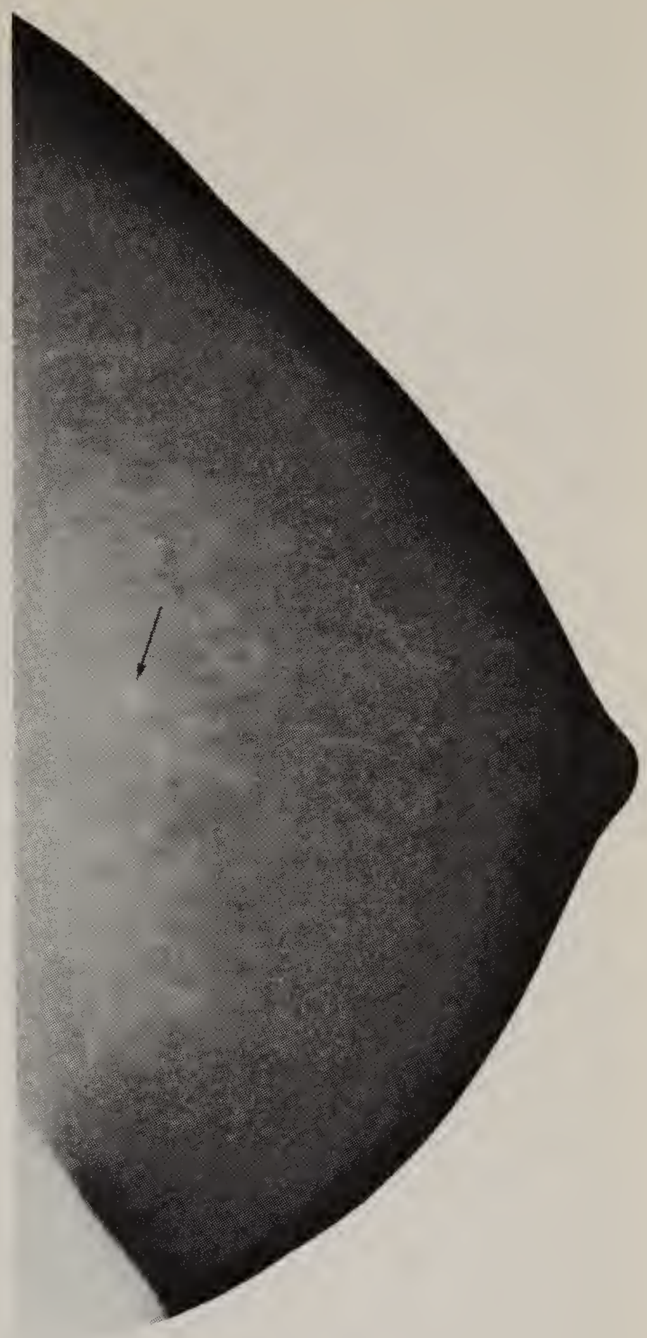

Fig. 4.—Seventy-seven year old female with clinically normal left breast six months following removal of right breast for obvious carcinoma. A 6 mm. carcinoma is shown above. This lesion was not palpable before surgery nor was it palpable in the amputated breast. (Egan, R. L.: Mammography, Springfield, Charles C. Thomas.)

3. Mammography also has a role in patients who have a definite palpable lesion. These include the very large and perplexing group of patients in whom one or more cysts of the breast are present. Figures 6 and 7 describe the role of mammography in fibrocystic disease.

Among these patients with a definite mass are those who refuse biopsy. Frequently, the evidence of potential malignancy has been shown on the films, and when this possibility is carefully explained to the patient, prompt acceptance of the necessary diagnostic surgery usually follows.

4. Finally, there is a group of unrelated problems in which mammography is of value. It is valuable in determining the cause of metastatic disease in patients where the primary lesion is unknown. This study is particularly helpful considering that this is the most common malignant lesion in women. It is also helpful in the very large breast, which is difficult to palpate, as well as in the cystic breast. It provides a permanent, easily reproducible record of the inner architecture of the breast for future reference.

Some comment should be made on the use of this examination as a so-called cancer check-up study in asymptomatic women. Witten[6] has found that in 5,014 asymptomatic women over the age of 40,

Fig. 5.—Sixty-nine year old female with vague nodules in the area of the areola. These have been present for an indeterminant number of years. The physical findings were not striking. They were felt to represent benign lesions. Films show an area of ductal dilatation and some enlarged vessels as well as the nodules. More specifically, small punctate calcifications are seen which are pathopneumonic of carcinoma. An infiltrating, intraductal lesion was discovered at surgery. (Egan, R. L.: Mammography, Springfield, Charles C. Thomas.)

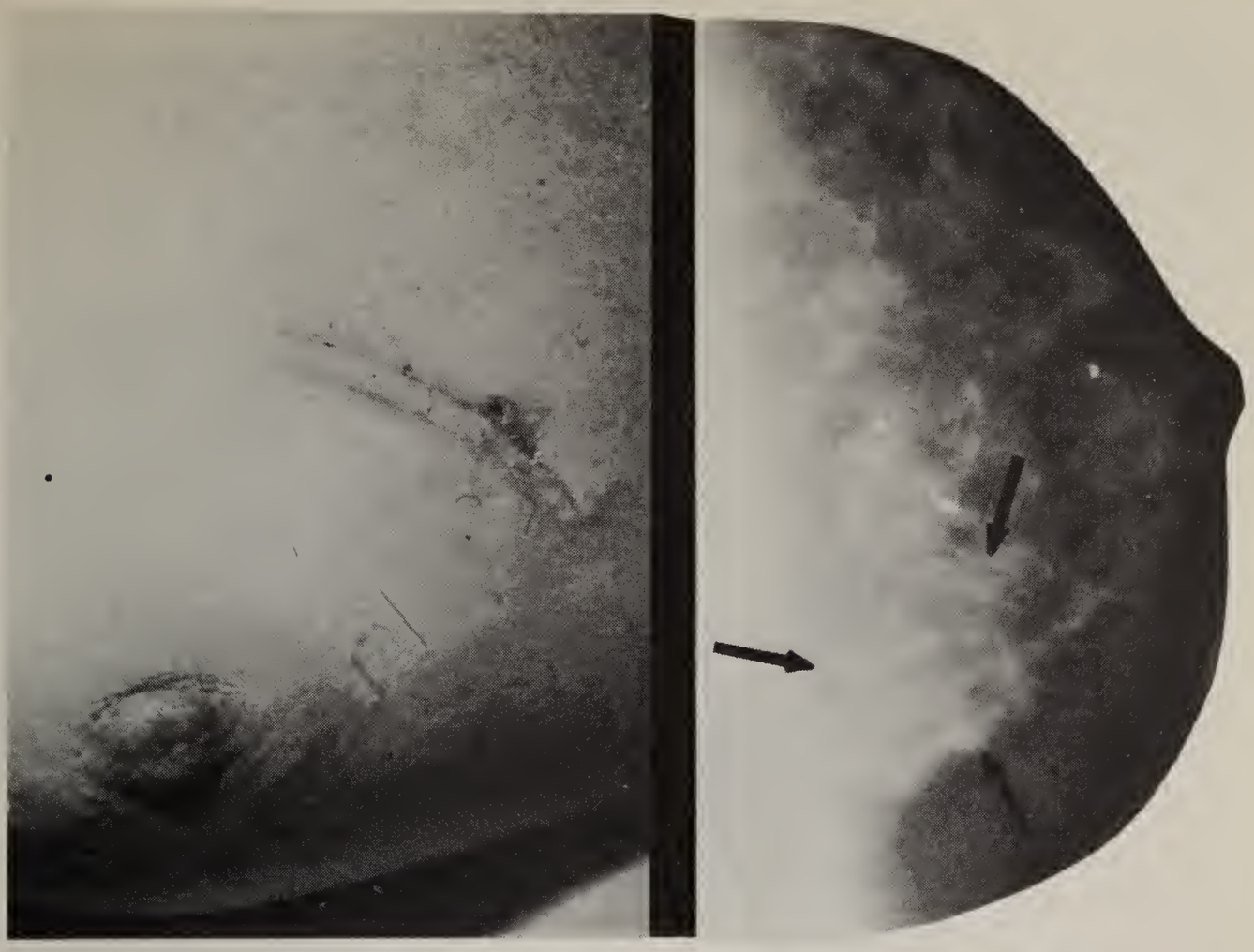

Fig. 6.—This patient has had at least one biopsy, which was benign, as evidenced by the presence of a solitary scar on the breast. Multiple lesions are palpated on physical examination. The patient is known to have fibrocystic disease. These lesions do not feel appreciably changed to the patient. In view of their apparent benign nature, should one of them be removed or should they be watched? The mammogram reveals at least three or countable cysts of moderate size. The black arrows show an area of irregularity adjacent to one of the large cysts, which on surgery was found to be a malignant neoplasm It is in cases such as these, that biopsy of the most suspicious protion of this nodular breast can be carried out with a high degree of assurance that the pathologist will receive the proper tissue for study. (Egan, R. L. and Linsay, J. P.: Breast Disease Lecture.)

only 8 preclinical carcinomas were evident. This is a case-finding rate of 1.6 per thousand. After the menopause, this figure rises to perhaps 0.3% or 0.4%. When symptoms are present, no matter how minor or vague, this case-finding rate also rises. There is a current study on the feasibility of surveying large numbers of asymptomatic women between the ages of 40 and 64 years.[7] The value of mammography in these cases, both as a qualitative and quantitative study, has by no means been established. The difficulties involved in training the large numbers of radiologists and technicians required, in addition to the substantial cost in comparison to mass screening for pulmonary tuberculosis, make it unlikely that it will become a widely used screening procedure in the near future.

The study has its sources of error as does any radiographic or laboratory procedure. About 90 per cent of the errors are traced to improper radiographic technique. Interpretive errors are usually the result of inflammatory conditions, such as, infected cysts or chronic abscesses, and fat necrosis mimicking malignant neoplasm. Errors of omission include very small lesions that are not seen, or perhaps not included on the film. Small malignant masses can be close to, or very adjacent to, benign disease; and this is often a source of difficulty. Geller,[8]

in a series of 408 cases noted a concurrence of 85 per cent. This was a specificity of 88 per cent: a normal mammogram, when at surgery a benign condition was found as indicated. There was a sensitivity of 79 per cent: malignant disease reported on the film, and malignant disease found by the pathologist.

Fig. 7.—A solitary mass, which has been present for about nine months, is noted in a forty-nine-year-old female. Clinically this was a benign cyst on palpation. Films reveal the cyst and also a nearby small carcinoma shown by the arrow. At surgery, the cyst containing greenish, brownish fluid was removed. Palpation of the wound was normal. On the basis of the mammogram, sharp dissection was carried into the area indicated by the arrow, and a 1 cm. carcinoma was uncovered. This case demonstrates how a large cyst can clinically obscure a small carcinoma, and how it is often difficult to find a small carcinoma in the presence of fibrocystic disease even at the operating table. (Egan, R. L.: Mammography, Springfield, Charles C. Thomas.)

CONCLUSION

When the uses and limitations of the study are kept in mind, where does the study fit into the group of diagnostic procedure used in the management of breast disease? It certainly does not take the place of history or physical examination. It should not take the place of a first biopsy of a dominant mass. It is often helpful in arriving at a decision to biopsy or not to biopsy when physical findings are uncertain, and selecting the biopsy site so that the pathologist is supplied with the proper tissue for study. Once the decision to biopsy is made, it is possible to conserve operating room time by knowing in advance, with a fair degree of certainty, the probable length of the procedure to be undertaken. It is a useful adjunct for diagnosis of breast problems. □

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HISTOLOGIC CHANGES IN THE TRACHEA FOLLOWING TRACHEOSTOMY

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Thomas E. Griffith, M.D.[2]
George M. Hass, M.D.[3]

INTRODUCTION

The mucous membrane alterations in the trachea observed at varying intervals after laryngectomy were recorded in a previous paper.[1] In the present survey we have analyzed tissues obtained at autopsy from the tracheobronchial tree of patients who, for various reasons, had undergone tracheostomy prior to death. For the most part, these tracheostomies were of fairly short duration. The findings were then compared to those observed in tissues obtained at autopsy from patients who had *not* undergone tracheostomy prior to death. Varying degrees of ulceration, denudation and infection were present to a far greater degree among patients who had undergone tracheostomy than among those who had not had this procedure.

There were 27 patients who had tracheostomies prior to death, and 44 patients without tracheostomies. The clinical records and autopsy protocols were studied in an effort to establish possible relationship to the histologic changes observed in the lower respiratory tract mucosa.

Various causes for alterations in the mucous membrane of the tracheobronchial tree have been listed. Recently, particular attention has been directed to the effects of tobacco and environment.[2,3,4,5] The experimental work of Hilding on the tolerance of the respiratory mucous membrane to trauma is fundamental and pertinent to this clinical report.[6] Plum and Dunning, after studying the signs of trauma to the trachea and bronchi due to aspiration catheters, proposed certain modifications in technique designed to minimize these tissue-damaging maneuvers.[7] As will be seen, some of the findings in the present study can probably be attributed to the effects of aspiration procedures.

FINDINGS IN PATIENTS WITH TRACHEOSTOMY

Ulceration of the Carinal Apex

A definite pattern of ulceration of the tracheal bifurcation was seen in 8 of the 27 patients in this group (Fig. 1). It is difficult to attribute this finding to anything but the manipulative procedure which accompanies the usual type of routine catheter aspiration employed in the care of patients with tracheostomies.

From the Department of Otolaryngology and Bronchoesophagology and the Division of Pathology

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Fig. 1.—This photomicrograph illustrates an acute ulcer covered with a mound of fibro-purulent exudate on the apex of the carina. Note that the destruction of the mucosa is accompanied by denudation of all except the basal layer of epithelium of one primary bronchus with fair preservation of the epithelium of the other primary bronchus. The group of pathologic changes was found quite frequently in the tracheotomized patients. In this instance the tracheostomy was of eight days' duration. H&E stain X50.

Ulceration, Denudation and Infection

As might be anticipated, some degree of denudation and infection of the mucosa was seen in association with the ulceration described above. In fact, 10 of the 27 patients exhibited these changes. Bacteria and fungi could often be identified in the involved areas.

Denudation, Repair and Regeneration

Associated with denudation of the mucosa were evidences of repair and regeneration in 10 of the 27 patients. This pattern has been previously described by Hilding.[6] The beginning of this process of repair can be demonstrated shortly after injury has taken place (Fig. 2).

Metaplasia

The finding of metaplastic epithelium was present in 9 of the 27 patients and could be seen most often in those whose tracheostomies were of 5 days' duration or longer (Figs. 3, 4, 5). In this group, however, there were 3 patients who had previously undergone X-ray therapy (Table I).

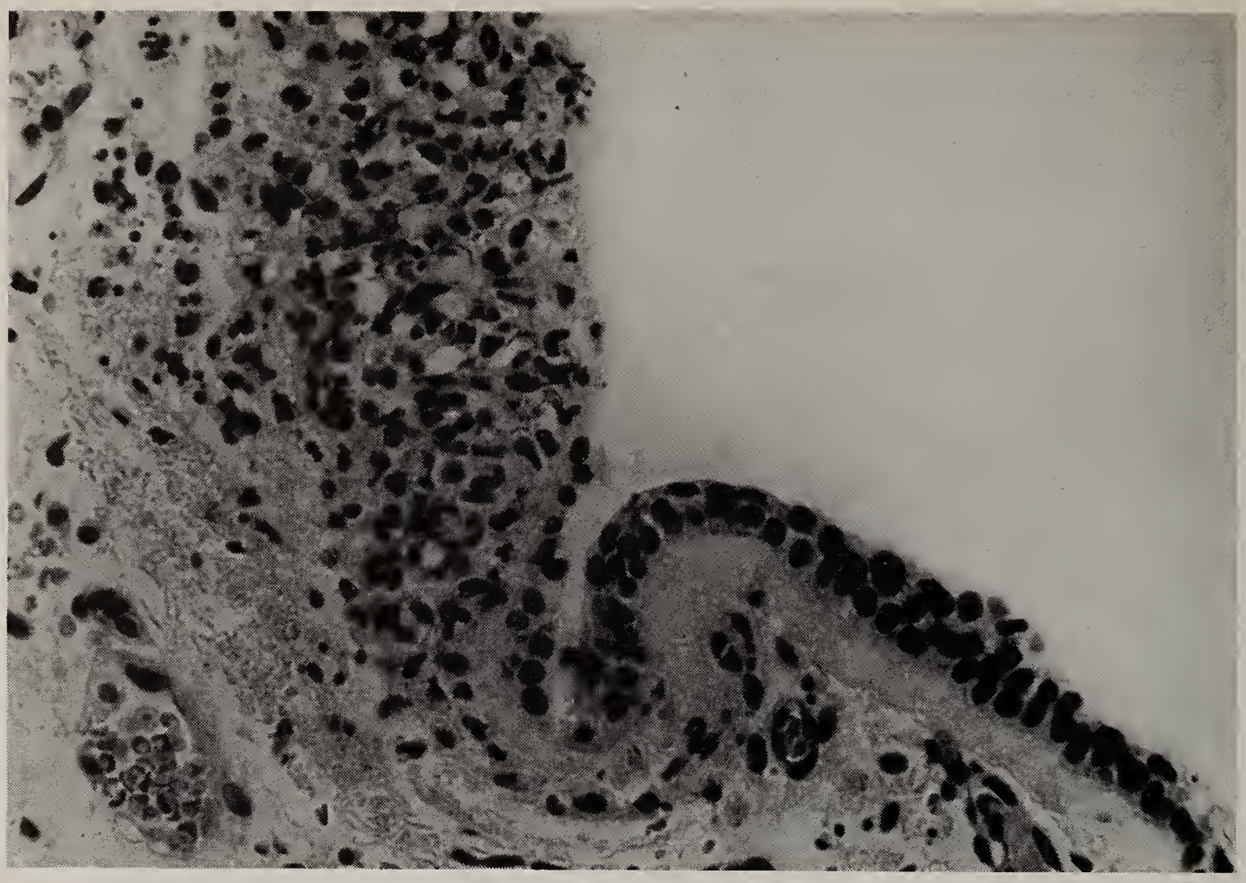

Fig. 2.—This photomicrograph illustrates a common type of epithelial repair following superficial ulceration and denudation. To the left is a lesion where the epithelium and basement membrane have been destroyed with excitation of a heavy leukocytic infiltration in the subjacent tunica propria. To the right the ciliated columnar and goblet cells have been denuded with preservation of the basal epithelium and basement membrane. Cells arising by division of the basilar cells have acquired, at times, squamous shapes and are oriented in a direction parallel to the basement membrane. This patient died following cardiac surgery on the second day following tracheostomy. H&E stain X330.

Chronic Inflammatory Reaction

The presence of inflammatory changes in the superficial and deep layers of the submucosa was demonstrable in 8 of 27 patients.

Miscellaneous Findings

The epithelial layer could be demonstrated to be intact and normal in only 1 of the 27 patients in this series. Autolysis of the epithelium was observed in 4 specimens and eosinophilic leukocyte infiltration was seen in 2 patients. The clinical histories in these latter 2 patients did not yield any explanation for the finding.

Control Group

In this group of 44 patients who had come to autopsy without tracheostomies, the absence of ulceration of the tracheal bifurcation is particularly noteworthy. Only a relatively small percentage of

Table 1.
Summary of Principal Histologic Changes

	Tracheostomy (27)	Control (44)
TRAUMATIC		
Intact Epithelium	1	34
Ulceration, Denudation, Infection	10	7
Carinal or Unilateral Bronchial Ulceration	8	0
Autolysis	4	9
REPARATIVE		
Denudation, Repair, Regeneration	10	0
Metaplasia	9 (3 x-ray therapy)	5 (1 x-ray therapy)
MISCELLANEOUS		
Fibrillary Basement Membrane	3	3
Chronic Inflammation	8	30 (19 severe) (11 mild)
Eosinophilic Leukocyte Infiltration	2	4 (3 diabetes)

the patients (7 out of 44) showed evidence of ulceration, denudation or infection and in none were there signs of regeneration or repair of the mucosa.

The fact that intact epithelium was found in 35 of the 44 specimens is of interest (Fig. 6). Autolysis (Fig. 7) and metaplasia were also observed (Table 1).

SEQUENCES IN REPAIR AND REGENERATION

The most common mucous membrane complication of tracheostomy seems to be denudation of the epithelium. Ulceration and infection often follow denudation and may be localized at the carinal apex (Fig. 1). Repair of the mucosal layer seems to take place in a fairly characteristic manner but is recognized more easily when ulceration and infection do not occur.

Fig. 3.—This photomicrograph shows a reparative metaplastic epithelial reaction in the trachea. As is the rule there is an inflammatory cell infiltration in the tunica propria and an indistinct basement membrane. Evidence for ultimate replacement of this type of epithelium by normal pseudostratified ciliated respiratory epithelium remains largely speculative. This patient, a 61 year old man, died, following cardiac surgery, 13 days after the tracheostomy. H&E stain X130.

The first evidence of repair following surface denudation can be seen most easily when only the tall superficial layer of ciliated and goblet cells has been destroyed. The intact basal layer may then show cells undergoing mitotic division within 24-48 hours, restoring first the tall ciliated epithelium and subsequently the goblet cells (Fig. 2).

When the denudation involves the entire thickness of the original respiratory epithelium, first evidence of repair can be seen in the migration of squamous epithelium from the basal layers at the margins of denuded portion or from the ducts of the sero-mucus mucosal glands. (This sequence was also demonstrated by Hilding in the experimental animal.)[6]

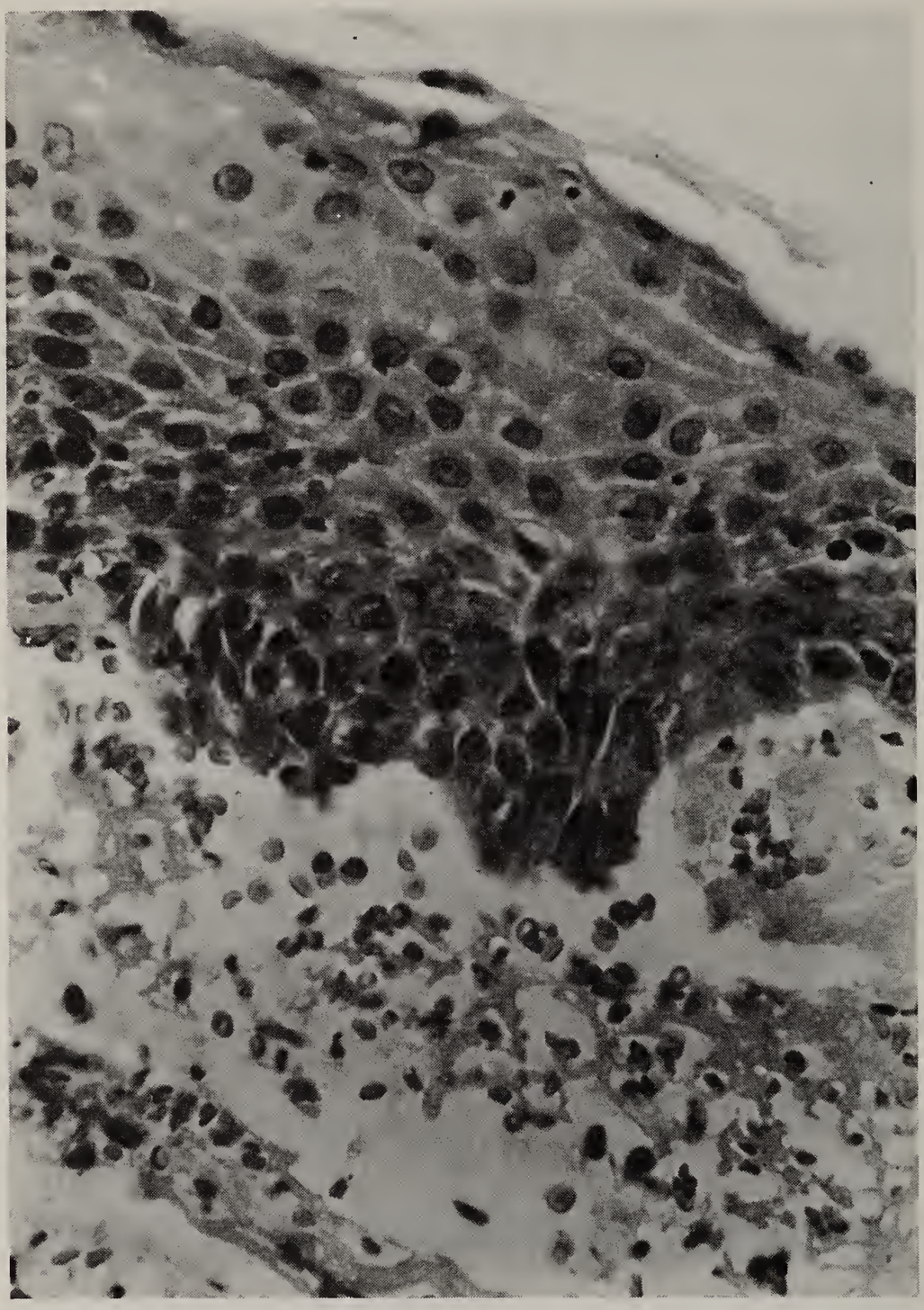

Fig. 4.—This photomicrograph shows an advanced type of epithelial metaplasia in the repair of tracheal mucosa. The basement membrane has been destroyed and the basal layer of the epithelium separated from the tunica propria by fluid containing many polys. The epithelium is several cells in thickness and the orientation resembles that which is customary for the epidermis. Whether this degree of metaplasia is reversible is unknown but reactions of this type often precede neoplastic transformations. This patient had a history of extensive irradiation for carcinoma of the esophagus. The tracheostomy was of 10 days' duration. H&E stain X330.

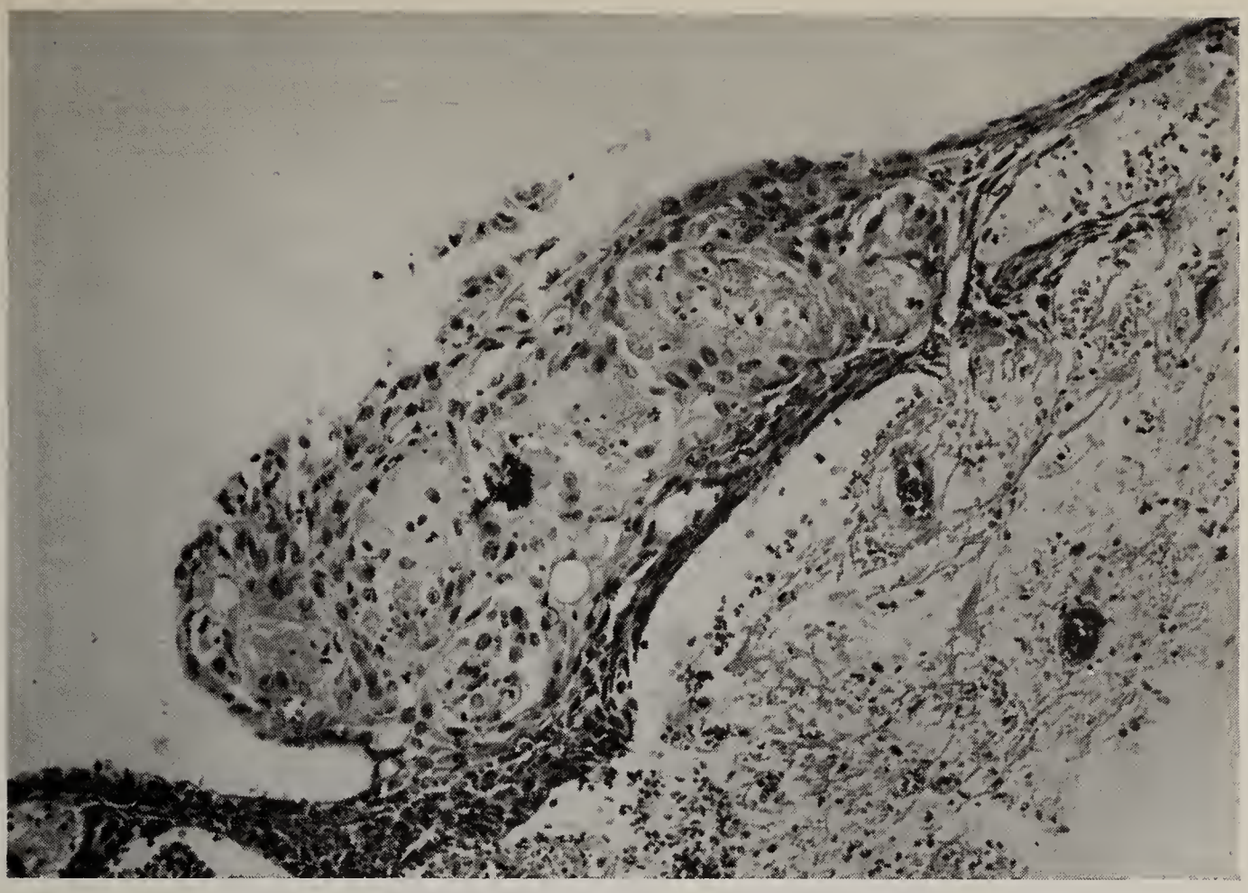

Fig. 5—This photomicrograph shows a very atypical metaplastic epithelium. Note that, as usual, the tunica propria has severe changes referable to prior persistent inflammation. The basement membrane has been destroyed. The regenerating epithelium of the trachea has formed intraepithelial "pearls" closely resembling arrangements encountered in the early stages of epidermoid carcinoma. It seems unlikely that the degree of metaplasia shown here is reversible to a normal respiratory ciliated epithelium. This is from the patient described in Figure 4. H&E stain X130.

When covering of the area takes place, there follows continued proliferation of these cells to form a multilayered epithelium which resembles squamous non-keratinizing or transitional epithelium (Fig. 3). Such epithelium may persist in multilayered form or may undergo three modifications: 1) modification of the superficial cells into columnar ciliated cells with retention of an underlying multilayered epithelium (Fig. 8), 2) degeneration and desquamation of the superficial cells with subsequent restoration of normal pseudo-stratified epithelium, and 3) persistence of the transitional stratified multilayered epithelium with an increasing tendency toward keratinization of the superficial layers (Fig. 4). □

SUMMARY

The histologic changes occurring in the lower respiratory tract following tracheostomy have been analyzed.

Specimens of trachea, carina and primary bronchi were obtained at the autopsy examination of 27 patients who had tracheostomies prior to death. Comparable tissues were obtained at autopsy from 44 patients without tracheostomies.

Intact epithelium was observed in only 1 of the 27 patients with tracheostomy. In the control group, 34 of the 44 patients exhibited an intact epithelial layer.

Carinal or unilateral bronchial ulceration was observed in 8 of 27 patients with tracheostomy and in one of the control group.

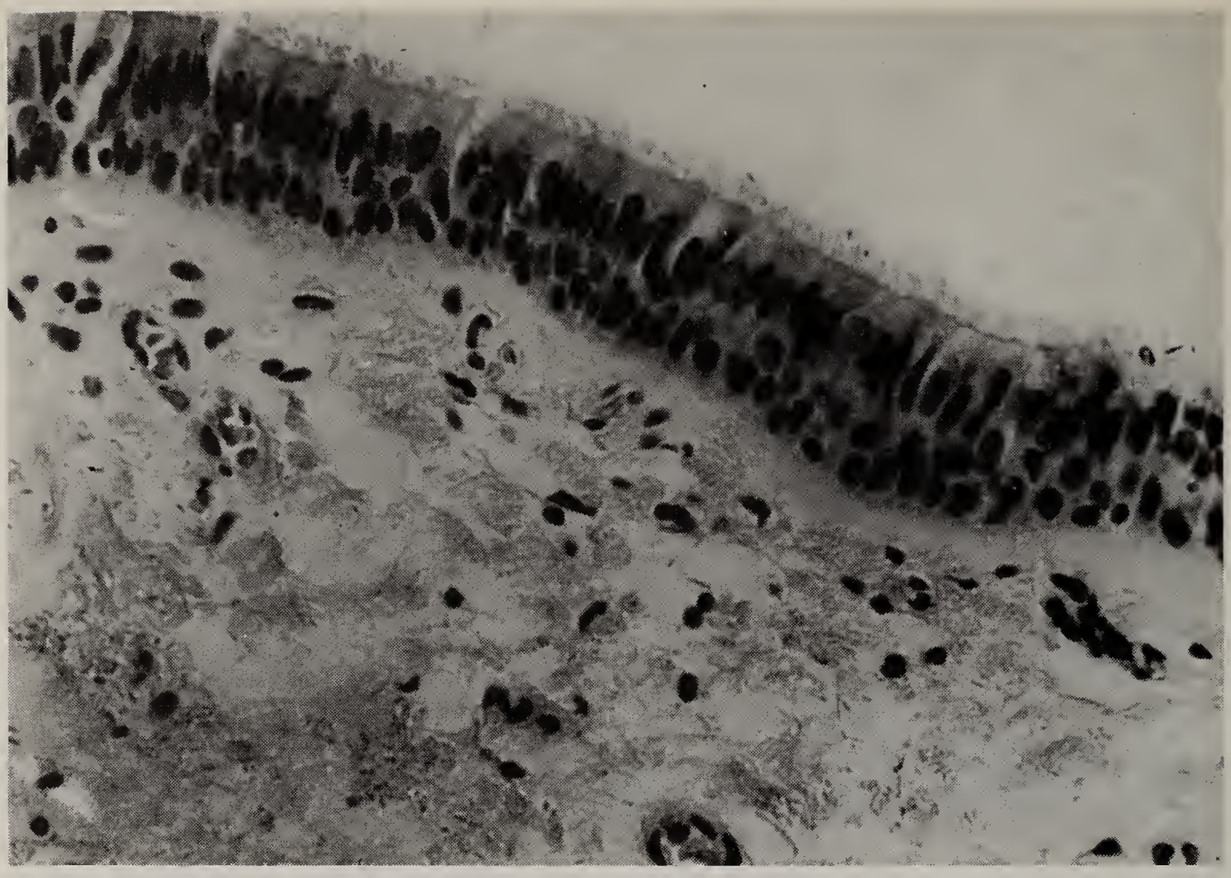

Fig. 6—This photomicrograph shows excellent preservation of normal ciliated pseudostratified epithelium, characteristic of the mucosa of the trachea, carina and primary bronchi. Note the cuboidal and blunt columnar basal layer of cells resting on the basement membrane. As these divide and differentiate, they replace the more superficial elongated ciliated and goblet cells which normally have a limited life-span. H&E stain X300.

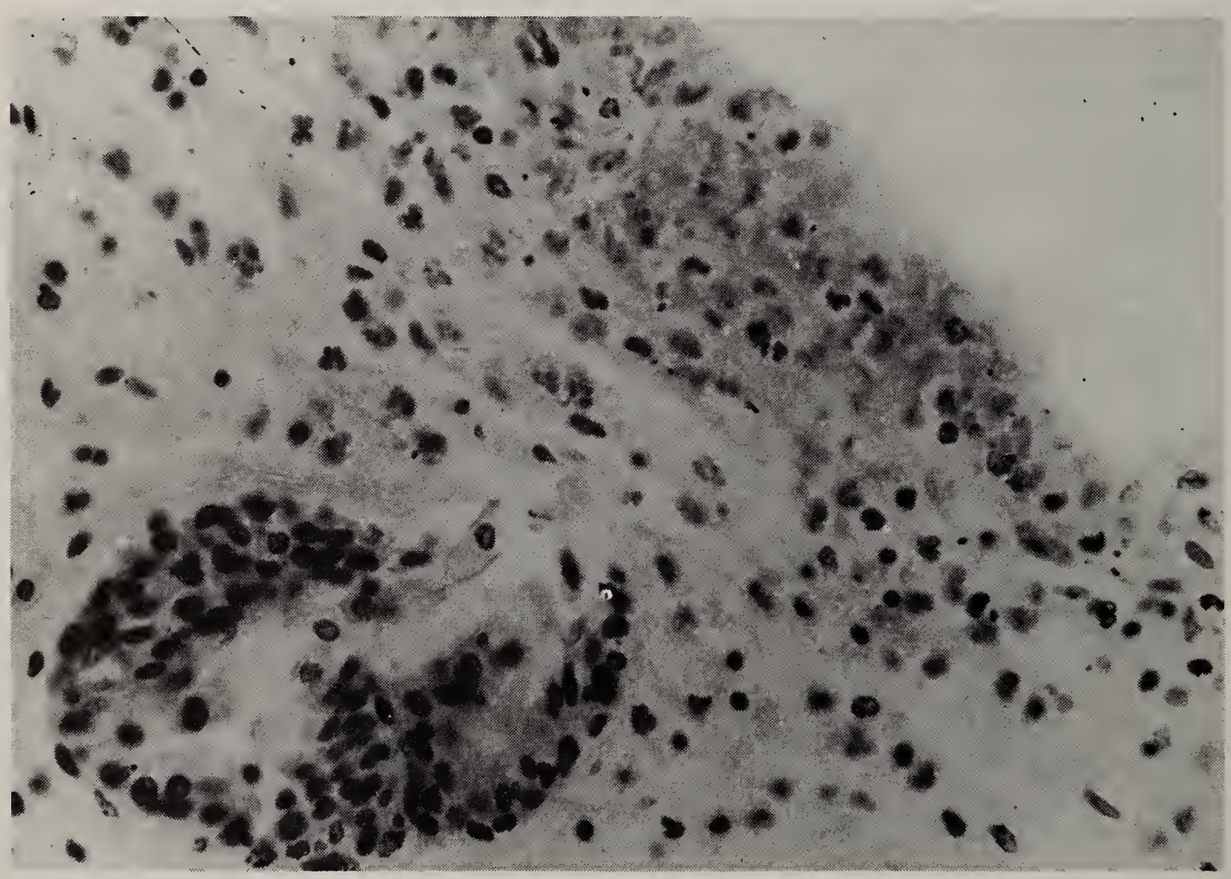

Fig. 7—This photomicrograph illustrates the absence of the epithelium of the trachea, carina or primary bronchi. At times it was difficult to distinguish between loss of epithelium due to infection, denudation or postmortem autolysis. Evidence of autolysis, presumably due in part to aspiration of gastric juice, is conspicuous here as indicated by the lack of sharp microscopic detail superficially and the progressive increase in the sharp staining of nuclei at increasing depth in the mucosa. H&E stain X330.

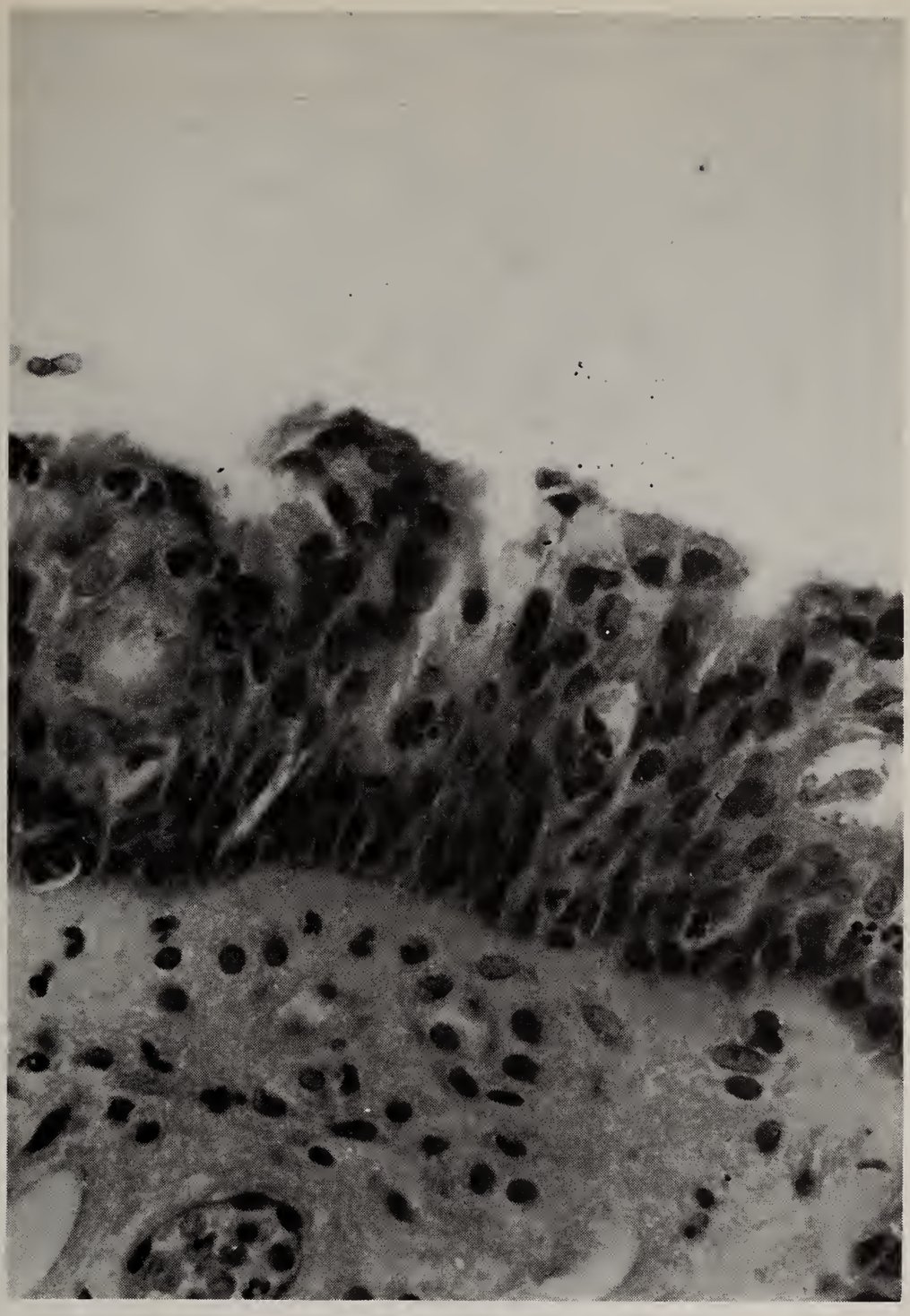

Fig. 8—This photomicrograph illustrates an abortive attempt at reversal of a metaplastic reparative epithelial reaction to a pseudostratified type of respiratory epithelium. Note the indistinct basement membrane commonly accompanying metaplasia. This is covered by an atypical layer of epithelium, six to eight cells in thickness. The most superficial layers have undergone an irregular differentiation into blunt ciliated cells. At a later stage in repair of this type, goblet cells make an appearance. This patient died following surgery, 11 days after tracheostomy. H&E stain X330.

Various degrees of ulceration, denudation and infection in the lower respiratory tract were observed in 10 of 27 patients with tracheostomy and in 7 of the 44 controls.

In the reparative process, regeneration of epithelium was observed in 10 patients with tracheostomy and in none of the control group. In the repair, metaplasia of the respiratory epithelium often occurred. The extent to which this might persist or be promptly reversed remains uncertain.

The regenerative process, metaplasia, chronic inflammation and other mucous membrane changes observed in this study of the lower respiratory tract have been recorded and analyzed. □

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CORONARY ARTERIOGRAPHY

GUY R. MATTHEW, M.D.[1]

INTRODUCTION

Knowledge of the nature of anatomic derangements should be complementary to existing methods of evaluation of those patients with suspected coronary artery abnormalities. Coronary arteriography, which is the *in vivo* roentgen study of the opacified coronary arterial system, is one approach to gaining this information.

Coronary angiography is conducted at this hospital according to the method developed by Sones,[1] which consists of cine-recording of the selectively opacified coronary arteries. Early studies of the coronaries were largely unsuccessful, primarily because of inadequate filming techniques and lack of effective volumes of contrast materials in the areas of interest. Many investigators have subsequently developed new and original methods of improving coronary filling,[2] among which is the method of Nordenström.[3] This technique was designed to enhance coronary opacification during supravalvular aortic injection by controlled elevation of the intrabronchial pressure. This subject has been reviewed earlier in the Bulletin.[4] Concomitant with the development of these newer techniques has been the introduction of better tolerated contrast media. It seems likely that the basic principles of arteriography, which include maximum deposition of the opaque medium as close as possible to the point of interest with rapid filming in several projections, are best satisfied by the method of Sones.

From the Division of Radiology and Nuclear Medicine

Presented at the Chicago Surgical Society Clinical and Scientific Program at Presbyterian-St. Luke's Hospital on February 5, 1966

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By standard brachial artery cutdown under local anesthesia, a specially designed radiopaque catheter is introduced into the ascending aorta in retrograde manner. The catheter is tapered near the tip and is curved, thereby providing a "finger" which facilitates selective catheterization of each of the coronary ostia. The catheter manipulation is observed on the television monitor of the image-intensified fluoroscopic system. Both the EKG and arterial pressure may be continually monitored and recorded. Selective entry into both the right and left sides has been the rule. Three to six milliliters of contrast material are injected by hand syringe during each of multiple injections, attempting to record the anatomy in several projections. Renografin (76%) is the opaque medium of choice at present. Transient EKG changes are observed following injection, but the patient usually relates no subjective sensations. The film recording is achieved with a 16 mm. camera mounted atop the image intensifier. The filming speed is 60 frames per second. Since the television monitor allows observation of the information being recorded on film, the examination may be conducted to allow optimum positioning of each individual case. The illustrations are examples of representative cases. They point out the difficulties in reproduction of isolated frames from cine studies, examinations which are intended primarily as rapid motion studies. It is obvious that there is wide congenital

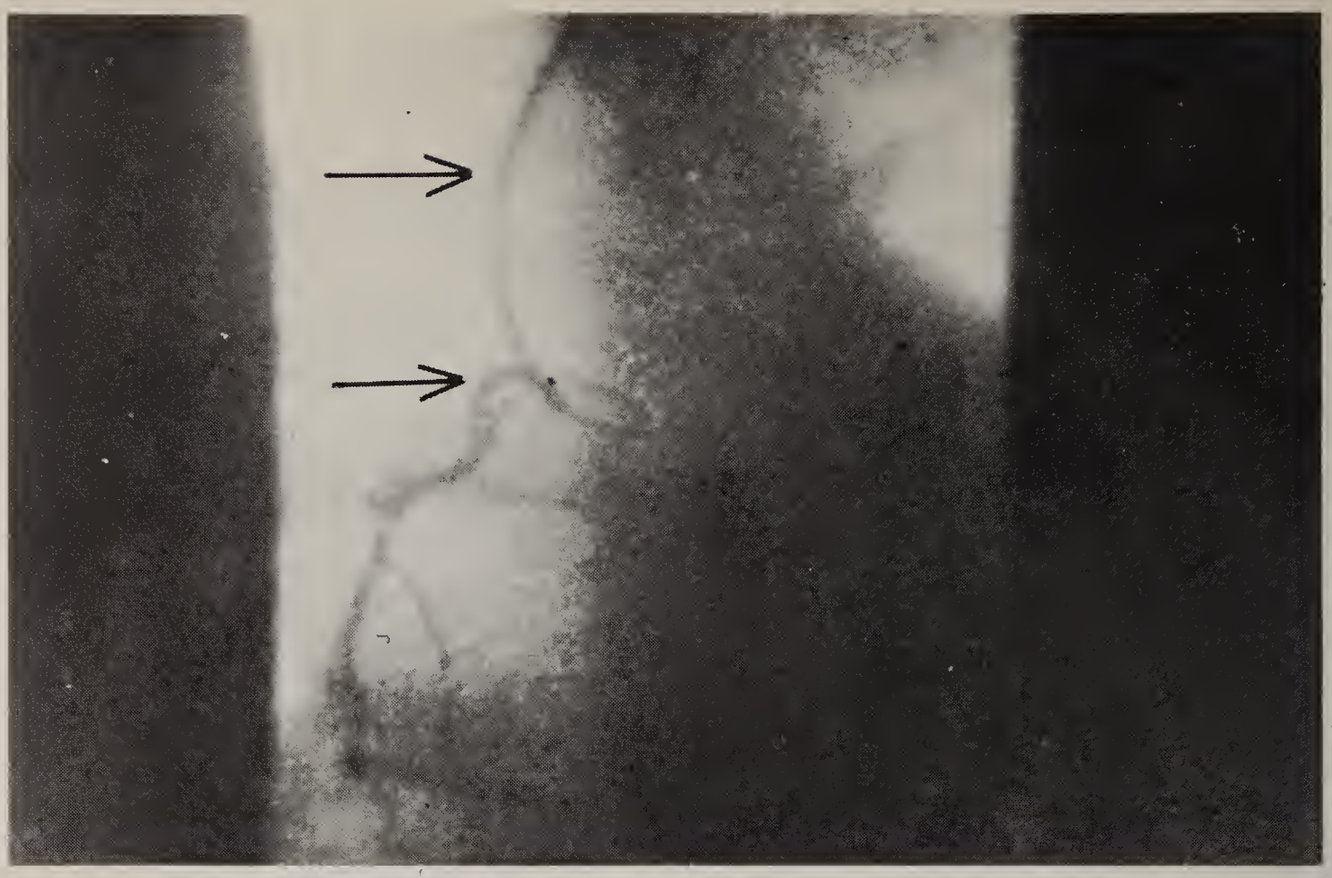

Fig. 1.—Selected frame from a cine strip illustrating a normal right coronary artery. AP projection. The catheter (upper arrow) is in the ascending aorta with its tip in the proximal portion of the coronary artery (lower arrow).

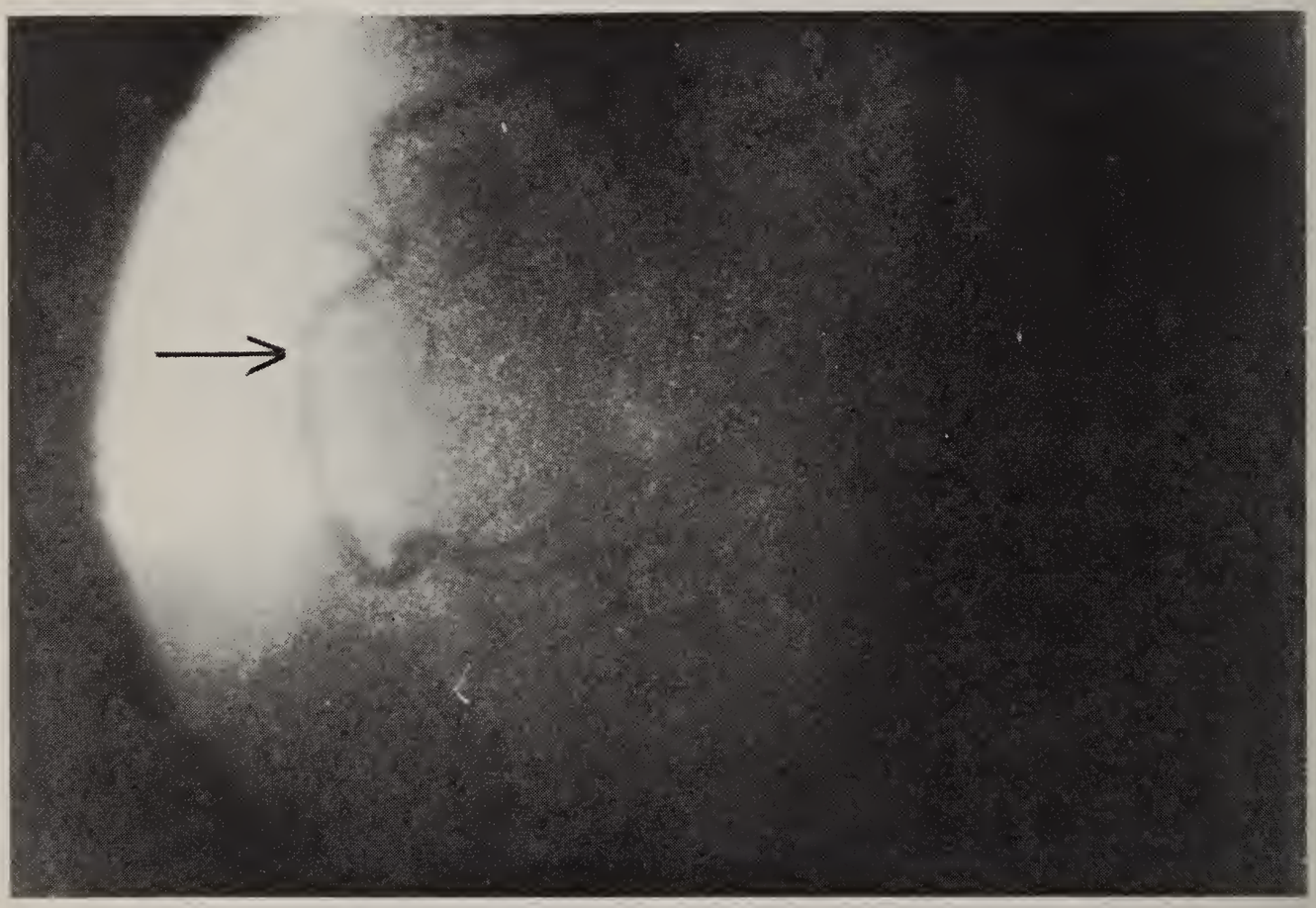

Fig. 2.—Another right coronary artery. LAO projection. There is a short area of narrowing in the mid-portion (arrow).

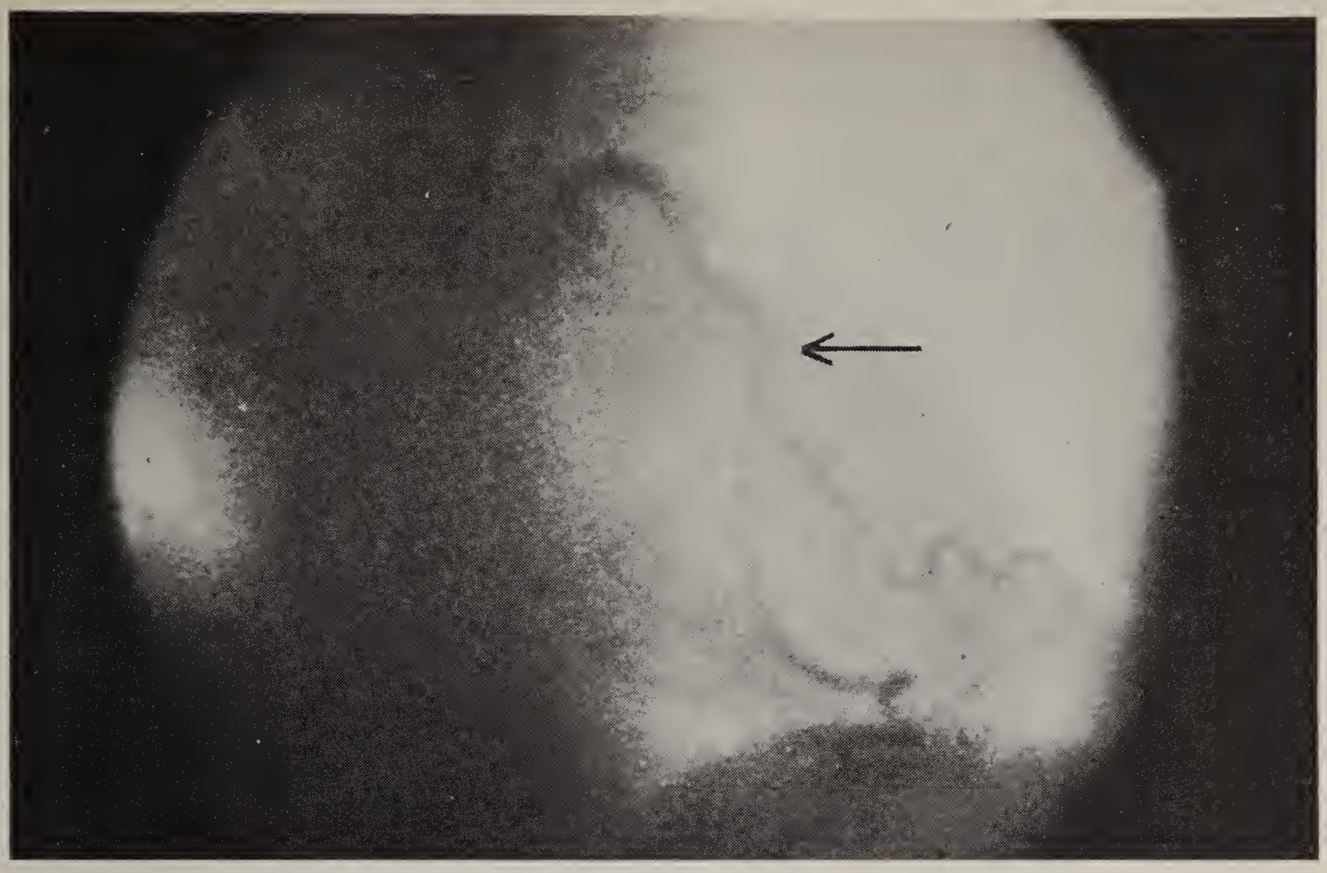

Fig. 3.—Normal left coronary system. AP projection. The circumflex division (arrow) is predominant in this case.

Fig. 4.—Same case as Fig. 3. LAO projection. The smaller anterior descending branch (arrow) courses anteriorly in this view.

Fig. 5.—Preoperative study of a patient with a completely occluded proximal right coronary artery (arrow). Subsequent frames demonstrated collateral opacification of the patent artery distal to the localized block.

Fig. 6.—Postoperative study of the patient illustrated in Fig. 5.—There is now free flow through the entire coronary artery. The localized widening (arrow) represents the vein patch at the site of the endarterectomy.

variation in the caliber of the individual coronary arteries, as well as in their branching.

The examination has been conducted as a joint effort between the Division of Radiology and the Cardio-Respiratory Section of the Division of Medicine. Chest pain has been the common symptom of those patients studied thus far. We have attempted to determine the presence of coronary arteriosclerosis, and whether it is localized or diffused. We have also studied two patients post-operatively to evaluate the surgical revascularization procedures performed.

Thirty patients have been studied, the last twenty-seven by selective cine-angiography. There have been two deaths, one due to myocardial infarction and the other to a non-responsive vaso-depressive episode. There has been one other myocardial infarction, non-fatal but with prolonged morbidity. There have been no instances of ventricular fibrillation. Five patients have undergone surgical revascularization procedures. One of the operated patients is illustrated in Figures 5 and 6. This patient experienced dramatic relief of his crippling angina pectoris.

It is apparent that there are many unanswered questions related to this examination, including the relationships of narrowing to flow[5] and ischemia. It is, indeed, with considerable caution that the results are interpreted, but it seems reasonable that the anatomic data obtained may be of value in the assessment of patients with coronary artery disease. □

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REVIEW ARTICLE

REPLANTATION OF LIMBS:
Experimental and Clinical Review

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INTRODUCTION

An occasional scene in any hospital emergency room is the arrival of a patient carrying a dismembered anatomic part, desirous of its replantation to the original site. Although the surgeon is often anxious to replace the severed part, and occasionally attempts it, the results are generally disappointing. The hazards of replantation prompt most surgeons, therefore, to accept substitutive therapy such as a mechanical limb.

For several hundred years by fantasy in art and literature[35] the regrafting of limbs has been contemplated. It was not until May 1962, however, that the first successful replantation of a completely severed limb, an arm, was achieved. Since then more than 30 other traumatically amputated extremities are known to have been returned to their original sites with varying degrees of success.

EXPERIMENTAL HISTORY

Spontaneous autotransplantation of biologic tissue is not unknown in the human. It has been observed in such instances as metastases, endometriosis, pseudomyxoma peritonei, and splenosis. Conditions necessary for the transplant to survive appear to involve healthy transplant and donor tissue, freedom from infection, and adequately re-established blood supply. Some tissues have their own special requirements for continued survival; skeletal muscles require an intact nerve supply; bone requires mechanical stress; gonads need correct local temperature for proper function; while some tissues appear to have hormonal requirements. After replantation, the transplanted tissue may survive, be destroyed and regenerate, or be permanently altered by substitution.

The ultimate measure of success in any replantation is, of course, the complete return of function to the replanted tissue. Blood vessels, skin, endocrine glands, bone marrow and other less organized tissues can be minced into small pieces and freely transferred into highly vascular beds with minimum of tissue loss. Complex organs, however, must depend on the re-establishment of blood flow before any degree of survival can be expected.

With the exception of a not fully authenticated successful limb replantation by two legendary Syrian physicians, Cosmos and Damian, in 400 A.D.,[29] the

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priority for the technique of experimental limb replantation goes to Halsted.[17] In 1887, he successfully transplanted the hind limb of a dog from one side to the other leaving the main artery of the transplanted extremity intact until union between the muscles and other divided tissues had taken place. Completely free organ replantation, however, did not become a reality until 1902 when Carrel[8] developed a successful technique for anastomosing vessels. This method was the first to show any lasting degree of vascular patency. Soon after, in 1903, Hoepfner[21] reported a high limb amputation followed by an attempted replantation while experimenting with arterial anastomoses. This transection-reimplantation procedure was modified in 1931 by Reichert and used to investigate extremity transplantation, lymphatic regeneration and circulatory balance of the limbs.[33,37,38] The relative successes in the entire field of organ transplantation and replantation since that date can be related to the improved application of vascular techniques. The ever-increasing desire to replace defunct essential organs with those from another individual has become so intense, however, that much of the experimental study has been unwisely directed toward homotransplantation before the basic problems involved in autotransplantation and replantation have been thoroughly understood.

In 1906 Carrel and Guthrie[9] replanted successfully the first completely severed hind limb of a dog. Fifty hours later it was necessary to sacrifice the animal because of a massive edema and coldness of the limb. The replantation followed only a brief period of ischemia. They described the limb as appearing "normal" following the surgery, but soon after the animal developed edema of the extremity and increased temperature. No further descriptive detail is given. In 1912, in providing an application for his technique of blood vessel surgery, Guthrie again described an experimental limb transplant which survived the initial surgery. This limb separated on the tenth day.

Russian workers first became involved in limb replantation in 1940 when Khenkin[23] reported two animals with autotransplanted limbs living forty-one and one hundred and twenty-two days. Later survivals of several years were observed by a number of Russian authors: Mazajev, Vishnevaki, Petrova, Levchuc and Lapchinsky.[23] The last investigator reported outstanding results at the Fourth Tissue Transplantation Conference in 1960. He had replanted a dog's limb, in 1954, following amputation with a nonsterile axe. Six years later the dog was demonstrated to have a full return of function and could stand on the limb and jump.

Lapchinsky studied cold preservation of living tissue and concluded, on the basis of tissue culture, that tissue changes following up to 24 hours of cold storage, remained reversible. The majority of his animals subjected to prolonged periods of ischemia died soon after surgery. This difficulty he ascribed to a toxic effect occurring in the operated dog soon after the re-establishment of circulation to the ischemic limb. He described the dog as becoming excited, with a pulse and respiratory rate increase, increased intestinal activity, and the occurrence of muscular convulsions. The blood pressure fell gradually with marked depression of all vital function followed by death within 5 to 12 hours. These toxic effects were not observed, however, when thrombosis interfered with flow through the reanastomosed femoral vessels. He also noticed that the severity of the shock depended upon the mass of tissue subjected to ischemia and did not observe shock following autotransplantation of kidneys. This would agree with Harmon's[19] work in tourniquet shock, i.e., that shock is produced by ligation and delayed release of an entire limb of a dog but not by ligation of only a paw.

In contrast to Lapchinsky's theory of toxicity, Eiken[13,14] related their high incidence (40%) of immediate death in dogs with replanted limbs to the local complications of marked limb swelling. He showed an extravasation of the edema amounting to a very significant part of

the fluid portion of the animal's blood, collected in the amputated limb. He proposed that this fluid loss caused the ultimate shock-state of the animal. Although a number of earlier authors have offered a similar hypothesis, the results of preventing this accumulation of edema by encircling the limb with plaster casts,[15,22] splints,[3] pressure dressings,[36,42] or tourniquets,[12] has failed to produce a significant improvement in the morbidity and mortality figures. In addition, the infusions of plasma or other colloids[43] into the animal in amounts equal to the losses into the limbs, have also failed to offer marked success.

It has been shown that an ischemic limb becomes devoid of measurable levels of glucose within four hours of the beginning of anoxia.[44] During this same interval both pyruvic and lactic acid levels become progressively elevated. It is possible, therefore, that Lapchinsky's "unknown toxin" may represent an accumulation of these anaerobic metabolites. We have observed that when blood is recirculated through a limb following ten hours of ischemia and returned to the systemic circulation, the animals develop immediate and frank shock with 100% mortality.[31] In addition, the blood returning from the recirculated limb is markedly acidotic, probably as a result of some of these anaerobic metabolites. If the acidosis is corrected by treating the animal with alkali buffers prior to, and after recirculation of the limb, this mortality can be decreased to less than ten per cent.

As previously observed, shock does not occur while the femoral vein is occluded.[23] Likewise, short periods of ischemia fail to result in shock.[31] These shorter intervals of ischemia would be likely to result in the production of lesser quantity of anaerobic metabolites, a level which the animal would be capable of tolerating.

The use of hypothermia appears to decrease significantly the rate of this metabolic breakdown of ischemic tissue.[1,31] In addition, irrigation of the tissue vasculature, preferably with infusions of heparin and saline also helps to remove some of these anaerobic products prior to release into the general circulation.[31] The limit of ischemia tolerated appears to be related to the duration of the obliterations of the blood supply and the temperature.

It is difficult to develop a protocol by which to study the effects of surgical replantations. While total ischemia can be produced experimentally by complete amputation of the limb, additional complications of femoral vein thrombosis are frequently encountered following the replantation. This complication has been reported as great as 77% in MacDonald's series.[26] In addition, even though the femur can be made stable enough for the animal to stand on following a complete amputation, it becomes difficult to study adequately the functional recovery after the nerves have been severed. Therefore, a variety of pseudoamputation methods have been developed to produce ischemia without completely amputating the limb. Those described in the literature include: multiple ligatures of the visible arterial supply;[7] ligation of the femoral vein with its inherent limb congestion;[7] rubber band tourniquet ligation for small animals[1] and Esmarch bandages for larger ones;[43] and finally the use of constricting clamps.[12] The common problem to all of these methods is that total ischemia can never be achieved. Also, the proportional degree of ischemia varies from species to species depending upon the amount of protective musculature. In the unlikely event that all of the soft tissue vasculature were occluded, there would still remain a significant rate of blood flow through the bone marrow of the femur. This flow has been shown by Galanti[16] to range from 11 to 13 cubic centimeters per minute (medium sized dog) with the femoral artery ligated and the pressure at zero, up to 200 cubic centimeters per minute with the femoral artery open. This small percentage of flow may offer an extremely important variable since McFarlane[28] has shown that a minimal amount of blood flow

under ischemic conditions may be sufficient to prolong the survival of tissue by maintaining resynthesis of ATP.

In order to develop a totally ischemic yet post-operatively functional limb for evaluation, we modified some of the earlier procedures. In addition to completely transecting all musculature, the perineurium was removed from the femoral and sciatic nerves and the marrow cavity opened and packed with surgical wax, thereby occluding it. This left both intact nerves and a stable femur post-repair so that the animal could begin use of the limb as soon as awake from anesthesia. Early ambulation helped to prevent atrophy of the musculature from disuse and also helped to hasten the loss of edema when the lymphatics began to regenerate on about the eighth day. These modifications lead to a more adequate evaluation of the functional recovery of the limb following varying periods of ischemia.

We found the majority of the animals attempting to use the limb soon after regaining consciousness from anesthesia. Marked swelling, distal to the incision, began occurring by the end of the second day and was maximum by the tenth. The edema began to recede by the tenth day or earlier but did not usually fully disappear before the 16th or 18th day. The swelling both began first and receded in the area nearest the incision with the more distal edema lasting for an additional 5 to 7 days. An occasional animal developed transient perioneal palsy. Hair often started growing within the first week and normal limb hair growth followed rapid wound healing. Diffused muscular atrophy, distal to the level of the incision was first noted during the third week. This remained moderate in degree and full muscle development returned within two or three months. The animals generally stood on all four legs by the first or second postoperative day and began placing minimal weight on the limb with walking by the fourth day. An occasional animal would attempt to walk from the first day. Gradual return of weight was applied over a two to three week period. The decided limp, observed during the first month, gradually diminished by the third month and complete return of function—walking, running, and jumping, became possible. By the fourth to fifth month the animal was able to stand alone on the two hind limbs. The suture line became lost within the new growth of hair and the previous evidence of muscular wasting could no longer be observed.

Clinical studies of ischemia related to vascular injuries occurring during World War II have not defined specific limits whereby restoration of the blood flow will result in permanently functioning tissue. An arbitrary time limit following partial ischemia to an extremity has been set by DeBakey and Simeone at 6 to 8 hours.[11]

Although the use of a tourniquet is often a necessity to the surgeon, and especially a hand surgeon, the maximum safe period of ischemia has not been adequately defined. A period of one hour or less has been considered by Bunnell[4] to be within the safe period. He states that tissue develops a firm induration if periods of over two hours are used. Based upon clinical observations, McElvenny[27] reports seeing no ill effects after two hours. At the Cincinnati General Hospital[20] it has been an established policy that extremities are constricted for no longer than four hours. They report no complications when this maximum period is applied.

A review of the experimental work with ischemia also suggests a variance in the opinions of the investigators. Lewis[25] points out that the vascular demands of different tissues are not uniform, and that their susceptibility to permanent damage is not equivalent to the rapidity of their loss of function. For example, nerves lose their function long before muscles become inexcitable to a galvanic current and yet muscle is killed sooner than nerve by prolonged ischemia. According to his observations, muscle fiber death is probably assured in the warm limb, when deprived of blood for six

to eight hours, while nerves may recover following ischemic periods for as long as 20 hours. Skin was even more resistant to ischemia, tolerating six to twelve hours before developing the presence of wheals and blistering. Only after 24 to 48 hours of ischemia was gross muscle necrosis seen.

Lewis also studied survival of the cells of various tissues following death of the organism. Using a method whereby neutral red dye would diffuse into granules or vacuoles of live cells, he could measure the time of cellular death. Using this method, he demonstrated that cartilage and smooth muscle were alive at the end of four hours of ischemia (37°). He was unable satisfactorily to stain striated tissue. He concluded that the rapidity with which a cell dies is directly proportional to its anatomical distance from the capillary which nourished it.

A number of investigators have employed tourniquet ligation of the extremities of experimental animals to study the effects of ischemia. Bywaters[6] showed that myoglobin was released into the blood stream following ischemic crushing injuries of 3 hours or longer. These muscles also lost significant amounts of phosphorous, potassium, creatine and glucose. These losses appeared proportional to the degree of muscle damage produced by the crush.

Brooks clamped the aorta of rats distal to the iliac artery and studied the pathology of muscles made partially ischemic. Following 6 hours of clamping the muscles showed return of function within ten minutes of unclamping. After 17 hours of clamping the irritability of the muscle could no longer be elicited. Longer periods of ischemia caused large areas of muscle necrosis three and four days later.

Wilson and Roone[44] studying the development of shock following prolonged tourniquet application to a dog's leg, observed that dogs with extremities ligated for more than six hours died following an average survival of 25¾ hours. In his discussion of tourniquets and their use, Allen[1] reports that a chicken wing will tolerate at least nine hours of ischemia without effect. Muscular tongues of dogs and cats had full return of function following eight hours of ischemia. Rat legs recovered after 13 hours of ligation and the tail of a dog after 15 hours. Using hypothermia during the ischemic period of tourniquet ligation, he obtained survival of rabbit's legs after 52 hours of ice-water emersion. One must remember, however, that tourniquet ligation is not total ischemia of the limb. Nevertheless, the limit of partial ischemia tolerated appears to be a relationship between the duration of the obliteration of blood supply and the temperature.

Miller[34] studied delayed restoration of circulation to the dog's partially ischemic leg using the replantation technique. Following a delay of circulation for six to nine hours, 100% survival could be obtained. Only 52% of the limbs survived periods of 12 to 20 hours. Of the surviving limbs only 15% developed per primum healing. They also had a slow growth of hair and a poor return of function. One animal of the latter group formed an ischemic contracture resembling that described by Volkmann. Miller could not reproduce this type of contracture by compression or ligation of the femoral vessels.

Harman[18] studied the histologic changes of striated muscle following various ischemic periods. He described a new type of cross striation of the muscle fibers appearing after six hours of ischemia which involved a widening of the anisotropic segment of the fiber. This morphological change, he believed, represented an irreversible state, the consequence of the ischemic death of the muscle cell. While six hours of ischemia were necessary to develop this change in the rabbit limb, a period of only four hours would develop the same changes in the rat leg. A variety of pathological changes could be predicted in the limb depending upon the length of the ischemia. Three hours caused shrinking and weight loss of the muscle, four hours developed scattered infarcted areas of fibers. By 12 hours, 90% of the muscle fibers were affected. Within 24 hours,

the nucleus had disappeared through karyolysis. Muscular contractions were unresponsive to galvanic stimulation in 78% of the limbs after undergoing four hours of ischemia. This increased to 100% by six hours. If the ischemia was terminated at six hours, contractibility would gradually return over the next 24 hours. The degree of recovery paralleled the number of surviving histologically normal muscle fibers.

Another approach to the study of ischemic tissue concerns the possible mechanism for survival or death of the cells. In order for any living tissue to maintain a viable state, work has to be done. The creation of this energy is by chemical reaction. In an aerobic model, adenosine triphosphate (ATP) is hydrolysed to provide the chemical energy for the work of muscular contraction. The energy for the resynthesis of ATP is furnished by the breakdown of phosphocreatine. The phosphocreatine is then resynthesized by energy obtained by the conversion of glycogen to lactic acid. As long as the model remains aerobic the lactic acid can be oxidized to resynthesize glycogen.[7]

Following release of a tourniquet, applied to the rat's hind leg for two hours, LePage[24] showed that the limbs rapidly restore their phosphocreatine and glycogen levels to near normal. However, following a four hour period of ischemia, the reformation of these materials remained absent for several hours. These findings are similar to the rat experiments by Ballman and Flock[2] in which they found phosphocreatine to become hydrolysed and disappear from ischemic muscle within one hour. ATP disappeared more slowly. They suggested that any remaining phosphocreatine was used for the resynthesis of ATP, thereby delaying its disappearance for about three hours. With ischemia for less than three hours there was a gradual resynthesis of both of these compounds. Longer periods caused a rapid and total loss of measurable levels of inorganic phosphates. Following this loss, edema formed in the tissues. Muscles surviving four hours of ischemia appeared to develop nearly total gross necrosis. Sufficient cells remained alive, though, for the muscle to recover some functional capacity by two weeks. McFarlane and Spooner[28] found similar changes in the levels of ATP after the limb of a guinea pig was made ischemic with a screw clamp. They showed the threshold for failure of ATP resynthesis to be about five hours.

CLINICAL HISTORY

Although the case of an arm replantation by Malt and Harris of Boston in 1962 is cited as the first successful replacement of a completely amputated limb, other partially amputated limb replantations have previously succeeded. Though attempts have often been made to replant fingers and toes, the first major limb replantation of which we are aware was the nearly complete amputation replanted by Androsov of the Sklifosoosku Institute in Moscow in June 1951.[41] This met with partial success. It was over ten years before Yutaka [44] reported successfully reuniting an amputated leg in Nara-Kaw, Japan. Although tissue viability of the leg remained good, the patient continued to need crutches for walking.

Since the above cases, over 30 additional attempts are known to have been made to replant major extremities arising from injuries caused by a variety of industrial, motor vehicle and firearm accidents. Figure 1 indicates the various sites at which surgery has been attempted. Of these various sites, the wrist area would appear to be the most difficult. Here, multiple small arteries, veins, nerves, and bones must be isolated and re-joined in a very restricted operative

SITE	CAUSE				
	Motor Vehicle	Firearm	Industrial	Misc.	Unknown
Upper Arm	1	3	2	1	
Forearm	2	1	3	1	1
Wrist		1	2		
Hand	1		4	2	
Thigh	1				1
Leg	2	1	1		1
Ankle					1
Foot	2				

Figure 1. Site of Amputation and Cause

area. In addition, the technique of bone shortening, employed when the replantation takes place in the upper arm, is usually not possible as the joint involved is the carpal-distal radius and ulna. Thus, vessels may have to be anastomosed under greater tension than desired, thereby increasing the risk of thrombosis. It is because of these added difficulties that the successful wrist and hand replantations by Shorey and Schneewind [40] in Chicago and by Ch'en[10] of the Sixth Peoples Hospital of Shanghai are of particular importance. In the latter case, a 21-year-old Chinese machine operator lost his right hand and wrist at his work. So successful was his early recovery that by the sixth week he was able to write, knit and hammer with the replanted hand.

Many of the patients, soon after the replantation procedure, have developed vascular or other problems. Although sufficient arterial blood can generally be delivered to the extremity, the arterial-venous perfusion of the limb may be unsatisfactory. This may be because an insufficient number of veins have been rejoined, because venous compression has been caused by limb swelling or because of the natural lymphedema caused by the transection of the lymphatics. An occasional case has also been observed to develop a severe form of 'toxemia' soon after recirculation of the limb, similar to the shock-like condition previously reported occurring in the experimental animal studies. Although this phenomena has been reported less often than would be expected from the animal studies, this may be because the period of limb ischemia in the clinical cases has generally been shorter than in the experimental procedures. This 'toxic' condition seen in the post-replantation period appears similar to that observed by Bywaters and others[5, 39] following crushing injuries. These cases involved patients who had one or more extremities crushed by heavy weights during the bombing raids over London in World War II. Soon after the weight was released from the extremity approximately 30% of the patients developed a severe shock which was progressive till death. A number of others developed a transient shock-like state which they tolerated and went on to survive. This latter observation is similar to animal studies in which dogs were able to tolerate certain sub-lethal intervals of limb ischemia and survived following a transient period of mild shock.[31]

SURGICAL REPLANTATION

Evaluation

The most difficult decision faced when encountering a severed extremity should be whether to undertake replantation. The answer to this question can only be made after all physical and physiological aspects of the case are considered. Whereas most surgical operations concern only

the patient in this respect, replantation surgery must, in contrast, also take into consideration the physical and psychological capacities of the surgeon as well. It is of great importance that both the patient and the surgeon possess the mental capabilities to withstand the rigors of the multiple operations and years of treatment that might be required before the re-union can be carried to a functional success. If either party is incapable of fulfilling these requirements, the surgery should not be carried out.

Of equal importance is whether a *partially successful* replanted limb would be of more benefit to the patient than a *successful* prosthesis; should the patient be a laborer who primarily depends on manual strength to earn his wages, a prosthesis may well be of more value to him. A more difficult decision will be the case of the patient who uses the extremity for skilled or semi-skilled work. In general, upper extremity prostheses are available in such excellent selection to strongly consider their use in many cases. In the event of a high amputation of the lower extremity, however, an area in which good prostheses are not currently available, replantation might offer a better hope for successful function.

To be considered also must be the time required for returning the amputee to work. In general, this period can be expected to be longer when replantation is attempted than when the decision is made to close the stump and later fit a prosthesis. In the event of bilateral hand amputation,[37] a surgeon might often be tempted to replant at least one extremity.

While attempting to decide whether the replantation should be done, a further evaluation of the physical possibility of re-union can be made. When extensive areas of nervous, vascular or bony tissue are obviously missing, replantation should not be undertaken. Although any one of these problems might be correctable in a less complex surgical problem, their multiple appearance makes surgery, other than revision of the stump, contraindicated.

The first and most important treatment of the limb is immediate cooling. This can be readily accomplished by wrapping the severed part in multiple sterile towels and covering completely in chopped ice or placing it in a refrigerator. It is possible to leave the limb this way for several hours without causing structural damage to the cells. The hypothermia increases the lag phase of bacterial growth as well as delays the formation of anaerobic metabolism in the ischemic limb.

Whenever possible x-rays should be obtained of both the distal stump and the severed extremity. Thus, any additional fractures can be dealt with should surgery be undertaken. Also, any other x-rays necessary in confirming life-threatening problems such as hemothorax or pneumothorax should be obtained at this time. Other more routine films, however, should be left to a later postoperative occasion.

It has been assumed that survival of the replanted limbs depends, among other things, on the removal of thrombi from the microcirculation which might prevent adequate tissue oxygenation and adequate venous drainage. It has been shown from animal experiments [30] that good vascular clearing can be obtained as long as 21 hours following amputation when a solution of physiologic saline and heparin (100 milligrams per liter) is infused at the rate of 15 cubic centimeters per minute from a pressure height of 75 centimeters. This rate of flow has been suggested for limbs weighing two pounds and would need to be adjusted proportionately to the weight of the limb. This solution is best infused cold and should be continued until most of the blood is washed from the limbs. This will require between five and ten minutes in the average case. Although a variety of other thrombolytic and micromolecular agents have been studied none appear to be as satisfactory as the salineheparin mixture.

In order to minimize the ischemic interval to the limb, it would be highly advisable to have one operative team prepare the limb while a second prepares the stump. Minimizing the ischemic period of the severed extremity is highly important, for as has been previously

stated, prolonged periods may cause severe toxemia to the patient when the limb is re-circulated.

It is almost superfluous to say that absolute sterile technique must be adhered to during the procedure but sometimes the common-place is forgotten in the excitement of dealing with the unusual. With the exception of obviously damaged or avascular tissue, the debridement of the stumps should be minimal. After location and tagging of all paired structures, the fracture site must be stabilized. This is usually best accomplished by an intra-medullary rod. It is the rigid framework that will act as a focal point around which the musculature will be reconstructed, and it will prevent movement as anastomosis of the vessels proceeds. A two to three centimeter shortening of the bone at the fracture site, when possible, will allow for an easier approximation of the vessels. In addition, if the bones are cut on the oblique it will help to prevent rotation of the limb. Venous anastomosis should be completed before attempting the arterial repair. These vascular repairs can be performed by the Carrell technique or a modification. By completing the venous side first an adequate runoff is assured without the possibility of having to reclamp the arterial side. Recirculation of the limb should begin as soon as feasible. Just prior to recirculation, a systemic infusion of alkali buffers should be started and should be continued in sufficient quantity as long as necessary to prevent a base deficit of the patient. Once satisfactory circulation of limb is instituted the repair of the musculature and achievement of hemostasis can be performed at a more leisurely rate.

Although a good argument might be made for the delayed repair of the nerves at a later date, thereby permitting a shorter operation on a seriously ill patient, our feeling is that a primary repair should be attempted if the nerve does not show extensive injury. If this can not be done the ends of the nerves should be tagged together loosely so that they might be located more easily at the time of the secondary repair. Whether the repair is primary or secondary, the possibility remains great that a later excision of neuromal tissue may be necessary.

Leaving the skin and subcutaneous tissue unsutured to be closed by secondary intention when the wound is assuredly clean may have the additional advantages of shortening the procedure and allowing for the marked edema which will be expected to occur now that the lymphatics have been sectioned. Posterior splinting and arm elevation will help to minimize this edema until the new lymphatic channels begin to establish themselves about the 12th to 14th day.

In patients in which the ischemia-anoxia-acidosis mechanism can be related to a possible development of shock, the following protocol is suggested: a constant monitoring of the acid-base analyses; the use of buffer therapy; constant monitoring of the central venous pressure; volume replacement as needed (preferably plasma but blood if it is obvious that this has been lost; blood, however, offers several problems of its own, among them acidity if it has been stored); central arterial pressure; blood volume; serial urine measurements; and serum electrolyte studies. Ordinarily, the only drug therapy would be the use of antibiotics.

The final degree of limb function will depend upon the intensity with which re-education of the limb is approached in the early weeks. Passive exercises and muscular stimulation should be begun within the first few days after surgery to help prevent atrophy of the musculature and joint immobility. These measures should be supplemented with active exercises as soon as the limb is functionally ready.

Viability of the musculature will be known within a few days of surgery, neurogenic recovery not for several months. Difficulty will arise in making the decision to perform a delayed amputation in the case of a replanted extremity that is viable but does not show signs of adequate function because of fibrosis or insufficient neurogenic return. Each of these cases must be decided individually.

SUMMARY

The future of the limb replantation need not depend on new surgical techniques being developed but instead on the perfection of presently known skills for good muscle, bone, vessel and nerve repairs. We now know from experimental studies that both muscle and nervous tissue of extremities tolerate long periods of ischemia and yet are capable of returning to a viable state when re-perfused with blood. We also know that return of function is immeasurably aided by intense application of passive and active movement and muscular stimulation untill the nerves again retrace their original pathways.

New techniques for tissue storage such as the small organ oxygen-perfusion apparatus recently developed by Professor Nizet of Belgium for use with long-term kidney studies, and the use of vascular stapling machines, may help to lessen excessive periods of ischemia, thus reducing morbidity and permitting a better functional result.

One may conclude that although the accepted treatment for these rare traumatic amputations of extremities has previously been closure of the stump and the fitting of a prosthesis, a prothesis no matter how perfect is not an integral portion of the human body and does not fully take over the functions of the lost part. Present knowledge and technique suggests that we should in these unfortunate situations, therefore, evaluate such patients for possible reunion of the dismembered limb. □

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ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

Intrinsic Renal Mechanisms for the Regulation of Body Electrolytes in Man. D. Baldwin, A. F. Nibbe and T. B. Schwartz: *Metabolism, 15:4, p. 338-358, April 1966.*

Previous communications have demonstrated that sodium balance in normal man is regulated through two to five day cyclical fluctuations in urinary sodium excretion *J. Lab. and Clin. Med.* 55: 362, 1960); and that these periodic changes do not result from fluctuating adrenal steroid secretion (*Metabolism* 12: 1032, 1963). The present studies reveal that these cyclical fluctuations are derived in part from comparable variations in mean daily glomerular filtration rate, and in the daily filtered load, both in normal subjects and in an adrenalectomized cortisone-maintained patient. Small transitory increments in the serum concentrations of sodium and the anion of the loaded sodium salt contribute to this filtered load, and participate in the excretion response to loading.

During sodium phosphate ingestion, the fluctuations of urinary sodium excretion were significantly correlated with daily phosphate excretion. Comparable fluctuations in urinary sodium and phosphate excretion can be demonstrated in a parathyroprivic patient maintained with vitamin D therapy, indicating that the urinary phosphate fluctuations are not derived from changing parathormone secretion.

In contrast to sodium, urinary potassium excretion during potassium salt loading is unrelated to mean daily glomerular filtration rate. Daily potassium excretion is also unrelated to daily urine volume, whereas daily water excretion in subjects drinking water *ad libitum* is significantly correlated with daily sodium excretion at all but minimal sodium intakes, a correlation that persists even during potassium loading.

The Kidney in Experimental Magnesium Deprivation: A Morphologic and Biochemical Study. H. Battifora, R. Eisenstein, G. H. Laing, and P. McCreary: *The Amer. J. of Path., 48:3, March 1966.*

The earliest renal lesion in magnesium deprivation was edema of tubular epithelium accompanied by increased amounts of ionic calcium in the cytoplasm. Subsequently, apatite crystal deposition occurred in the pars recta of proximal convoluted tubules, loops of Henle and collecting tubules. These deposits were both extracellular and intracellular and occasionally formed casts. Early intracellular calcium deposits arose in the hyaloplasm or in lysosomes. Focal increase in numbers and enlargement of lysosomes possibly represented a response to damage to the nephron by the calcium deposits. Calcification of mitochondria was not observed and suspensions of isolated mitochondria showed no change in their calcium content. Mitochondrial calcification occurs in magnesium deficient rat sarcosomes and in renal mitochondria in vitamin D and parathyroid induced nephrocalcinosis. Only basement membranes calcify when calcium gluconate is given intravenously.

This is in contrast to the distribution of calcium in the cardiac lesion of magnesium deficiency and in other types of nephrocalcinosis. These morphologic and biochemical differences among the various types of abnormal calcification re-emphasize the role of the cell and its organelles in this pathologic process.

Transplantation Potential of Marrow Frozen at Programmed Cooling Rates. J. P. Lewis, M. Passovoy and F. E. Trobaugh, Jr.: *Ed. du Centre Nat. de la Recherche Scientifique, 73:78, 1965.*

The success of a marrow transplant is related to several factors, the most important being the repopulating potential of the graft and the effective control of immunological incompatibilities. The repopulating potential bears no relationship to the intensity of the rejection phenomena but is directly related to the stem cell content of the transplanted marrow.

The experiments reported in this paper were designed to study the effect of controlled rate cooling on the preservation of stem cells. Stem cells were assayed using bioassay based on the colony producing potential of hematopoietic tissue injected into lethally irradiated isologous mice. These colonies are comprised of developing hematopoietic cells, are grossly visible on the spleen and their number is a function of the number of viable stem cells injected. This bioassay yields quantitative rather than quantal data and is twenty-five times as efficient as animal survival assays.

Within the ranges studied, the rate of cooling to freezing, the duration of the pre-freezing plateau, and the temperature at which freezing was initiated did not affect marrow viability. However, stem cell viability *decreased* in a linear fashion as: (1) the post-freezing plateau was *lengthened* or (2) as the rate of cooling from freezing to −100°C was *increased.*

Hematopoietic Repopulation by Marrow from Congenitally Anemic (WBB6F$_1$-WW^v) Mice. L. F. O'Grady, J. P. Lewis, J. Schellmann, S. E. Bernstein, E. S. Russell and F. E. Trobaugh, Jr.: *Amer. Fed. Clin. Res., September, 1965.*

Substitution of the gene-pair WW^v for the normal ++ allele at the W locus in mice results in ovarian failure, black eyes with a white coat and a macrocytic anemia. The white blood cell count and platelet count are normal. In mice, successfully transplanted hematopoietic tissue develops as visible colonies on the spleen, whereas transplanted WW^v marrow rarely produces such visible colonies. This suggests there is either 1) an almost total absence of stem cells or 2) a basic defect in the early stages of hematopoiesis. Following 900r irradiation, non-anemic WBB6F$_1$ mice received either ++ or WW^v marrow cells. Nine days later spleens of recipient mice were removed, fixed, serially sectioned and the hematopoietic repopulation studied. Many small colonies were formed within the spleens of mice injected with WW^v cells suggesting that WW^v stem cells are not markedly decreased. A basic defect in the early stages of hematopoiesis of WW^v marrow was suggested by the following differences observed between ++ and WW^v colonies. ++ marrow produced large colonies adjacent to the splenic capsule, 63% of which contained erythroid precursors. WW^v marrow produced small colonies generally deep within the spleen, only 12% of which contained erythroid precursors. These studies provide an example of genetic mutation effecting stem cell differentiation and growth rate of transplanted marrow.

Genetic Influence on Repopulation and Differentiation of Transplanted Marrow. J. P. Lewis, L. F. O'Grady, S. E. Bernstein, E. S. Russell, and F. E. Trobaugh, Jr.: *Blood, 26:870, 1965.*

In mice, hematopoietic repopulation normally occurs in the spleen as visible colonies composed primarily of one cell type. The study of these colonies permits an evaluation of stem cell frequency and an estimation of rate of growth and pattern of differentiation in the early stages of hematopoietic repopulation.

In mice, the substitution of the gene-pair WW^v for the normal ++ allele results in a mouse with a white coat, black eyes, ovarian failure and a macrocytic anemia. Previously it has been shown that when hematopoietic repopulation is effected by marrow of WW^v mice, there are few if any grossly visible colonies on the spleen. Our studies were designed to investigate the nature of this defect in repopulation.

Non-anemic WBB6F$_1$ mice were irradiated with 900r and injected with marrow cells of either ++ or WW^v mice. Nine days later the spleens of host mice were removed, fixed, serially sectioned and the colonies of hematopoietic tissue counted and their cellular composition determined.

Marrow cells of the ++ mice produced large colonies which were near the splenic surface. More than one half of these colonies contained erythroid precursors. The WW^v marrow produced tiny colonies which were deep within the spleen and 12% of these colonies contained developing erythrocytes.

These data demonstrate that there is a serious defect in the early stages of growth and development of hematopoietic cells bearing the mutant gene-pair WW^v and suggest that the interaction of these genes markedly depresses the development of erythroid colonies and slows the rate of growth of granulocytic and megakaryocytic colonies. It further suggests that severe anemia may result not only from defects in the late stages of erythroid development but also from the early stages of erythroid maturation and hematopoietic repopulation.

Clinical Patterns of Tuberculous Peritonitis. E. K. Hudson: *Arch. of Intern. Med., February 1966.*

Tuberculous peritonitis continues to be a frequently encountered disease. The diagnosis is of obvious importance because of the therapeutic implications. Because of its many puzzling disguises the disease may require considerable perspicacity and persistence on the part of the physician.

Thirty-one patients diagnosed as having tuberculous peritonitis at the University of Illinois Research & Educational Hospitals between the years of 1953 and 1963 were reviewed. Emphasis was placed on the clinical and laboratory findings that point to the presence of this disease and on those factors which seemed most likely to prove misleading in making this diagnosis.

The history of exposure to tuberculosis, evidence of the disease elsewhere in the body, and studies of the ascitic fluid seem most helpful. Peritoneoscopy, biopsy procedures, or laparotomy may be the only means of establishing a proper diagnosis within a reasonable time. False positive cytology, cirrhosis, sole reliance on histologic interpretation, negative skin tests, and transudative ascitic fluid characteristics are some of the factors which may confuse the clinical picture.

The Importance of the Contribution and Timing of Left Atrial Systole. R. A. Carleton. M. Passavoy, J. S. Graettinger: *Clini. Sci., 30:151-160, 1966.*

Utilizing individuals with complete atrioventricular block who have undergone therapeutic implantation of pacing catheters, observations have been made on the left ventricular response to variable timing of atrial systole. It has been shown that for any given ventricular rate there is a hemodynamically optimal P-R relationship. These optimal P-R values are inversely related to ventricular rate; at a ventricular rate of 60, a P-R value of approximately 0.20 seconds is optimal, whereas at a ventricular rate of 100, a P-R value of approximately 0.15 seconds is optimal. The magnitude of the atrial contribution was estimated by the changes in ventricular systolic pressure. The atrial contribution was linearly related to ventricular rate, and achieved a mean value of 27% augmentation of ventricular pressure at a heart rate of approximately 100 beats per minute.

The Medical Lecture as an Art Form. R. W. Carton: *Jour. of Med. Educ. 40:12, December, 1965.*

A talk to medical students is only effective when it is handled either consciously or unconsciously as an art form. Its degrees of freedom are many: the effectiveness, wit, and ability of the speaker; his confidence and command of his material; the artistry and appropriateness of his slides and drawings; the skill of his audience in their role as an audience.

When these elements cannot be brought together successfully, the lecture should be dropped. When they can, the effect is powerful; and year later, long after the informational content has been rendered obsolete or perhaps forgotten, the strength of the presentation will still be alive as a force in the student's life and work.

Cardiac Pacemakers: Clinical and Physiological Studies. R. A. Carleton, R. W. Sessions, J. S. Graettinger: *Med. Clini. of No. Amer., 50:325-351, 1966.*

This paper represents a review of the use of cardiac pacemakers as they modify the pathophysiology of patients with complete atrioventricular block. The clinical management of such individuals is outlined, including the detection and correction of malfunction of the electronic pacemakers.

Overestimation of Left Ventricular Volume by the Indicator Dilution Technique. R. A. Carleton, A. F. Bowyer, J. S. Graettinger: *Circ. Res., 18:248-256, 1966.*

In this work, direct comparison of left ventricular volume, as estimated by the indicator dilution technique and simultaneously by the angiocardiographic technique, was conducted. It was shown that the indicator dilution technique grossly overestimates left ventricular end-diastolic and end-systolic volume. The reasons for this discrepancy were explored. Non-homogeneous mixing of indicator within the left ventricle is the major reason for these overestimates of ventricular volume.

Simultaneous Recording of Radiographic and Physiologic Data During Cardiac Catheterization. J. S. Graettinger and R. W. Sessions: *Amer. Heart Jour., 71:422, 1966.*

The method used for simultaneous recording of fluoroscopic and physiologic data in the Cardiac Laboratory of the Section of Cardio-Respiratory Diseases at Presbyterian-St. Luke's Hospital is described. The image from an Orthicon television camera, which views the intensified fluoroscopic image, is combined with that from a Vidicon television camera, which views the monitor oscilloscope, on which the electrocardiogram, intracardiac pressures, etc. are displayed. The combined images are viewable on television monitors and regardable on a television kinescope or tape recorder.

Implementing Improvements in an Outpatient Department. W. R. Tucker, I. R. Turner, J. C. Lashof, N. W. Ream, and J. J. Herman: *Arch. of Environ. Health, Vol. 2, pp. 22-27, July, 1965.*

"Implementing Improvements in an Outpatient Department," by W. R. Tucker, M.D.; I. R. Turner, M.T.; J. C. Lashof, M.D.; N. W. Ream, M.D.; and J. J. Herman, M.S.H.A., Chicago.

As a result of assessing the value of the periodic examination of outpatients undertaken by Lashof and Turner at Presbyterian-St. Luke's Hospital, it became apparent that the outpatient clinic itself required periodic evaluation. This led to change and innovation in the following areas: (1) broadening the scope of all patient workups to include two hour post-prandial blood sugars and sigmoidoscopy on all patients over the age of 40; (2) institution of biennial physical examinations for patients in the medicine clinics; (3) coordination of services in the management of patients in the medicine clinics under the control of one attending physician for each patient; (4) assignment of medical students to specific positions during their outpatient rotation; (5) establishment of a diagnostic index cataloguing the prevalence of diseases in the outpatient population; (6) establishment of a quarterly chart review by the physicians and students; (7) design of a mechanical system for the storage of medical and financial information which is yet to be implemented; (8) design of a medical care check list which is yet to be implemented.

It was not possible to document improvement in the level of medical care as a result of these innovations. This may be due in part to our inability accurately to define and measure the level of medical care. However, it was felt that such measures could lead to improvements in medical care.

Surface Uptake of the Azo Dye Luxol ARN by Human Platelets. R. M. Lycette, W. F. Danforth, J. L. Koppel, and J. H. Olwin: *Can. J. Biochem. 44: 161-170, 1966.*

Luxol ARN, a dye reported to complex with phospholipids, has been applied to human platelets. Under conditions of equilibrium involving platelet and dye concentrations it was found that dye uptake increased with increasing temperature, dye uptake decreased with increasing pH, and dye saturation of platelets could be achieved.

Evidence has been obtained to suggest that complex formation between dye and platelet hydrophobic groups occurs through adsorption probably complicated by chemical binding and that the dye is bound in a monomolecular manner. Based on this, the finding that no more than 16.8% of the total platelet phospholipid was involved in complex formation supports the conclusion that dye uptake may be limited to the platelet surface only. Additional support for this conclusion was provided by the absence of visibly demonstrable intracellular dye.

Application of a nonionic surfactant, known to disperse platelet aggregates, reduced platelet dye uptake, a finding that suggests a possible relationship between aggregation and surface phospholipids.

Fibromatosis of the Plantar Fascia: Surgical Indications and Design of Skin Incision. J. W. Curtin: *Jour. of Bone and Joint Surg., 47-A:8, p. 1605-8, December 1965.*

The same disease process causing the typical hand deformity known as Dupuytren's contracture is seen frequently in the foot. Failure of proper foot examinations, lack of symptoms and absence of toe contractures are reasons for the small number of reported cases.

In contrast to palmar fasciectomy where innumerable types of skin incisions are shown, the placement and design of incisions on the sole of the foot is absent from the surgical literature.

The purpose of the presentation is to report our experience in arriving at a proper and advisable skin incision that will allow adequate exposure of the plantar fascia and not jeopardize skin flaps.

Microcirculation: The Third Force. G. de Takats: *JAMA, 195:4, Jan. 24, 1966.*

There are definite and ever-growing applications of the knowledge of microvascular responses. Microcirculation has been the neglected "third force" in the cardiovascular circuit. In spite of the spectacular advances taking place in cardiac and major vascular surgery, tissue nutrition remains inadequate and cardiovascular repair is futile should microcirculation fail.

After defining the microscopic and ultramicroscopic areas involved, the acute and chronic forms of microcirculatory involvement are discussed. The behavior of microcirculation in various types of shock, during cardiopulmonary by-pass and after local injuries due to mechanical trauma, cold, burn and electricity are described.

In the chronic phase, the microangiopathies due to hypersensitivity, collagen diseases, diabetes, hypertension, gout, micro-embolism and microthrombosis are enumerated. Of the regional disturbances, cerebral, renal and splanchnic microangiopathy are surveyed. Postischemic, postsympathectomy and postphlebitic microcirculatory changes are presented.

All forms of treatment aim to improve and maintain adequate perfusion pressure through the microvascular bed. Increasing cardiac output, elimination of excessive vasoconstriction, desludging agents, antithrombotic and fibrinolytic drugs in the acute failure, anti-inflammatory, steroid and immunosuppressive drugs in the chronic failure are discussed. Proper selection and proper timing of these agents, some of which are powerful and may be contraindicated when ill-timed, are made on the basis of frequently repeated or continuously monitored tests for microcirculatory failure.

Adjuvant Chemotherapy. W. H. Cole, R. G. Mrazek, S. G. Economou, G. O. McDonald, D. P. Slaughter, and F. W. Strehl: *Cancer, 18:12, December 1965.*

There are numerous types of adjuvant chemotherapy—use of anticancer drugs at the time of operation. Four of them are discussed herein: 1) systemic administration of the drug, 2) instillation of the drug into the lumen of the bowel, 3) intrabronchial chemotherapy and 4) irrigation of wounds with anticancer agents. The rationale of adjuvant chemotherapy is based on several factors:

a. Experimental evidence suggests that anticancer drugs given at the time of cancer cell inoculation will minimize "take" and growth of the tumor;
b. Cancer cells are found in veins draining the tumor area;
c. Cancer cells are dislodged during operative manipulation; and
d. Cancer cells often lie dormant for years and in this slowly growing state might be susceptible to action by anticancer drugs.

Jejunal Obstruction Secondary to Enteric-Coated Potassium Chloride Therapy. M. A. Pomerantz, W. M. Swenson, S. G. Economou: *Jour. of The Amer. Geriat. Soc., Vol. XIV, 3:200-204, March, 1966.*

A case report is presented of a 59 year old woman who was treated for hypertension with an enteric-coated thiazide-potassium chloride preparation for one week. A single episode of epigastric distress lasting a few hours caused her to discontinue the medication. After six days, during which she remained symptom-free, she was admitted to the hospital for an acute episode of small bowel obstruction. Several attempts at conservative management of this were unsuccessful, and a celiotomy was performed. A single, intensely inflamed, stenotic segment of distal jejunum was found and resected. There was a narrow, sharply delimited, circumferential ulcer within the surgical specimen. The lesion appeared benign on both gross and microscopic inspection.

Small bowel ulceration caused by enteric-coated potassium chloride preparations has been reported several times since it was first recognized in 1964. The hazard incurred by the use of these drugs has been offset by their convenience and the low incidence of complications. Many patients taking thiazide compounds have required potassium supplementation beyond the amounts available from dietary sources.

The short exposure to the drug in this case, and the irreversibility of this lesion are emphasized.

Fiber-Optic Laryngoscopes, Bronchoscopes and Esophagoscopes. P. H. Holinger: *Annals of Otol., Rhinol. & Laryngol., December 1965, Vol. 74, No. 4, pp 1164-1166.*

Fiber-optic light transmission provides extremely effective illumination for endoscopic equipment. Using this as a basis, a series of laryngoscopes, bronchoscopes and esophagoscopes have been designed to take maximum advantage of this new system. All batteries, electrical connections and miniature lamps are eliminated. The light source is a 150 watt bulb with a self-contained reflector housed in a lamp box electrically isolated from the scopes. Light is transmitted by a fiber-optic cable to an oval fiber-optic carrier in the scopes. Special design features of the bronchoscopes and esophagoscopes include a new distal tip, a shortened proximal flare, and a respirator tube with an adaptor that will accept anesthesia apparatus. An air-tight window plug can be used interchangeably on all bronchoscopes and esophagoscopes for either positive pressure respiration or anesthesia during bronchoscopy, or for inflation of the esophageal lumen during esophagoscopy. A proximal two-power magnifying lens may be attached with or without the window plug. The laryngoscopes use the same source of illumination and short oval light-carriers. "Streamlining" the light carriers permits a smaller external diameter while increasing the internal working lumen of all scopes.

Telecobalt Therapy of Early Malignant Tumors of Vocal Cord. G. G. Hibbs, F. R. Hendrickson: *Radiology, 86: 447-449, 1966.*

The projected cure by telecobalt therapy alone of our first 100 cases of early carcinoma of the vocal cord is 91 percent. These were in patients who had lesions involving one or both movable cords. The method of analysis was the actuarial or life-table approach, which allows use of incomplete follow-up information to obtain an early prediction of the future success. None of the patients required a tracheostomy or laryngectomy for a complication of the treatment. All patients with persistent disease were cured by the subsequent laryngectomy.

Microsaccades and the Velocity-Amplitude Relationship for Saccadic Eye Movements. B. L. Zuber, L. Stark, and G. Cook: *Science, 150:3702, p. 1459-1460, December 1965.*

The maximum velocities of microsaccades (flicks) are an increasing function of amplitude of movement. Measured velocities fall on the extrapolation of the curve of maximum velocity versus amplitude for voluntary saccades and involuntary corrective saccades. Hence all these movements are produced by a common physiological system, or the characteristics of the movements are determined by a single dynamically limiting element.

Management of Catastrophic Reactions in Children. A. H. Norton: *Jour. of the Amer. Acad. of Child Psych. 4:4, October, 1965.*

The catastrophic reaction is a complex of defense mechanisms designed to ward off profound anxiety experienced by a person when massive forms of bodily insult threaten the whole structure of his lifelong adaptive and defensive patterns. The reaction occurs typically in individuals whose characteristic defenses have been predominantly counterphobic and who interpret any failure of function as destruction of their egos and death.

Four cases have been presented to illustrate a particular approach to catastrophic psychosis. In each case I have seen there is a premorbid personality structure in which the major adaptive-defensive constellation centers around using phobic-counterphobic mechanisms to protect against narcissistic injury. Characteristically this involves externalization of an internal conflict by phobic displacement, then mastery of it by counterphobic techniques.

The catastrophic reaction may be conceptualized as occurring in the following sequence. First, there is an increase of characteristic defensive patterns to ward off growing awareness of the threat to the body's intactness. Second, when mastery can no longer be achieved or sustained, a total ego disruption results which is expressed in the representational fantasy of annihilation. Third, the part frequently referred to as the "catastrophic reaction" is a restitutive attempt of the ego to survive by using primitive, often psychotic, mechanisms of denial, projection, withdrawal, and instinct reversal.

It must be realized that the primary stimulus for the catastrophic psychosis is an intrapsychic one, whereas the reaction to a cataclysmic event originates from external sources. Once removed to relative safety, the stress reduced, and the anxiety lessened, there is decreased threat of ego deterioration. The person subject to the catastrophic reaction, however, carries the potential cataclysmic event within him.

THE EDITOR'S PAGE

SURGICAL HERITAGE—1966

"To foster the development of surgery as a science" was the avowed purpose of a young society initiated in Chicago in 1900 by Doctor John E. Owens acting upon the suggestion of Daniel N. Eisendrath, M.D. Today, we not only pursue this lofty surgical objective but we are engaged in a continuing effort to cultivate its growth.

Early in 1900 a young Rush trained physician, Daniel N. Eisendrath, returning from postgraduate studies in Europe, prevailed upon Dr. Owens, a prominent St. Luke's surgeon and Professor of Surgery, to convene with a few prominent colleagues to discuss the founding of a surgical society. A preliminary meeting of the future Chicago Surgical Society was held shortly thereafter in the Chicago Athletic Club attended by most of the charter group of twenty-six surgeons. The more renowned included Drs. Christian Fenger, Nicholas Senn, John B. Murphy, Arthur Dean Bevan, Albert J. Ochsner, John E. Owens and L. L. McArthur.

Early in its existence, the Society also established the Morning Hospital Clinic Programs to add further impetus to the development of surgery in the city. These meetings have been held continuously to the present with the exception of three years during World War II. During the current year the Society has visited four metropolitan hospitals. On these occasions the members have had not only the chance to visit laboratories where research was in progress but have had the opportunity to discuss first-hand clinical and academic problems of mutual interest.

On Feburary 5 of this year, the Society attended the Morning Hospital Clinic and Scientific Program presented by the Presbyterian-St. Luke's Hospital. Five of the scientific papers presented by members of the hospital staff on that occasion have been selected and constitute the body of this issue of the Medical Bulletin.

Some readers might take issue with several conclusions drawn from these reports. Still others will concur. All, however, must applaud the underlying purpose of the Morning Clinic Meetings which, as expressed in the Society's constitution, is for "the cultivation and improvement of the Science and Art of Surgery. . . ." in Chicago.

FREDERIC A. DEPEYSTER, M.D.
Special Editor

BYTERIAN-ST. LUKE'S HOSPITAL MEDICAL BULLETIN

PRESBYTERIAN-ST. LUKE'S HOSPITAL

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THE SELECTION OF EPILEPTIC PATIENTS FOR TEMPORAL LOBECTOMY*

John R. Green, M.D.[1]

It is a very great privilege, I feel, to be invited here today to address you. Having served as extern, intern and as a resident in Neurology and Neurological Surgery at St. Luke's Hospital, commencing in 1939, there is that pleasant sensation of returning home to the people who are continuing to provide outstanding postgraduate medical education. I have never regretted the night in the operating room when Dr. Eric Oldberg invited me to enter the field of Neurological Surgery, and I esteem the personal friendship he is still providing.

The title of my talk, "The Selection of Epileptic Patients for Temporal Lobectomy," also stems from experiences and techniques taught to me initially by members of the St. Luke's Hospital staff and others, notably by Drs. Percival Bailey and Frederic A. Gibbs, in the Illinois Neuropsychiatric Institute of the University of Illinois Research and Educational Hospitals, during 1946 and 1947. Since then, there has been a renaissance of clinical and investigative study of the temporal lobe and its functions in the major centers.

The subject material has become increasingly important because it is now apparent that sclerosis of the inferomesial aspect of the temporal lobe (incisural sclerosis, Earle, Baldwin, Penfield[1]; mesial temporal sclerosis, Falconer[2]; or hippocampal sclerosis, Green and Scheetz)[3] is the most common focal epileptogenic lesion and is also the most favorable of the various pathological conditions from the standpoint of results from surgical treatment.[1,2,3,4] These conclusions have evolved slowly.

The patient is usually referred for consultation because of lack of response to medication. The following plan for the study of each patient has been developed:

1—General and Neurological History and Examination

The history of birth trauma or a period of coma associated with increased intracranial pressure due to trauma, infection, anoxia, toxins and other causes, at any period of life prior to the onset of psychomotor seizures or nocturnal convulsions, suggests the possibility of injury to the hippocampal gyrus and adjacent structures. The presence of low grade neoplasm, hamartoma or vascular anomaly must be considered if psychomotor epilepsy develops during the same period of life, for example between the ages of 10 and 30, without such history. Mesial temporal sclerosis may be found at surgery where no definite history of its cause can be elicited. Trauma or infection earlier in life may lead to more diffuse involvement including atrophic lesions and meningocortical cicatrices which

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*Presented as a Special Lecture on May 19, 1966, sponsored by the Skidmore, Owings & Merrill Lectureship Fund under the direction of the Alumni Foundation of Presbyterian-St. Luke's Hospital.

[1]Chairman, Division of Neurological Surgery, Barrow Neurological Institute, St. Joseph's Hospital, and Neurosurgical Consultant, Arizona State Hospital, Phoenix, Arizona.

TABLE I
SELECTION OF EPILEPTIC PATIENTS FOR TEMPORAL LOBECTOMY

I. Clinical Seizure Pattern:	with localization to accessible, excisable cortex
II. Electroencephalographic Localization:	corresponding to I
III. Cortical Pathologic Lesion:	corresponding to I
IV. Mental status:	compatible with I and its social effects
V. Stability of Localization of Epileptogenic Area, or its Progression:	particularly in children
VI. Failure of Other Methods of Treatment:	medical, psychiatric
VII. Good Surgical Risk:	general health, no or minimal neurological deficit to be anticipated from surgical excision

may become epileptogenic. There is also a need to consider a genetic etiology in patients presenting a focal form of temporal lobe epilepsy, regardless of age, according to the recent work of Bray and Wiser.[5,6] The physician must study each patient with great care before invoking a genetic explanation for a focal electroclinical seizure.

A description of the pattern of the clinical seizure in detail from the normal state, through the aura, if present, and seizure manifestations to the normal condition is obtained from the patient and from reliable observers who have witnessed the attacks. The patient may or may not recall an aura, cannot recall an automatism and may report that he has had a convulsion. From the history as obtained from the patient only, the initial impression of the examiner may be that the condition is idiopathic epilepsy.

The patient with psychomotor epilepsy will describe one or several of a variety of psychic symptoms, such as illusions of perception, visceral and olfactory sensations, dreamy states, and hallucinations of vision or hearing prior to becoming amnesic and having a convulsion. The informed observer may describe automatic behavior, groping movements, running fits, fumbling activity, smacking of the lips, and behavioral abnormalities, including assaultiveness, particularly if the patient is restrained. Noctural convulsions are common. Manifestations of psychomotor epilepsy have been described in numerous reports since the original delineation of this type of epilepsy by Gibbs, Gibbs and Lennox[7] in 1937.

Neurological examination is usually normal. However, hemiatrophy, visual field defects, and other abnormalities are carefully recorded as guides in localization. Medical disorders that might contribute to the seizures are searched for with the help of appropriate consultants and laboratory study.

TABLE 2
TEMPORAL LOBECTOMY
JULY 1948 TO MARCH 1965
Etiology (suggested by history)

Difficult birth, anoxia	22	25%
Trauma after birth	21	23.9%
Obscure causes	16	18.1%
Neoplasms	15	17%
Febrile convulsions during infancy including encephalitis, meningitis	14	16%
	88	100%

2—Psychiatric Evaluation

Psychiatric and psychometric studies are essential to the understanding of the behavioral, social and economic aspects of this disorder in relation to the postoperative management and results.

3—Neuroradiological Examinations

Skull films are taken to detect signs of asymmetry, previous injury, intracranial calcification, pineal shift or other abnormalities. A small middle fossa suggests injury to the temporal lobe with secondary atrophy of long standing. Pneumoencephalography and carotid

TABLE 3
TEMPORAL LOBECTOMY
JULY 1948 TO MARCH 1965
Surgical Pathology

Chronic atrophic lesions Inferomesial sclerosis	44	50%
Meningocortical cicatrices	15	17%
Neoplasms	15	17%
Obscure causes	14	16%
	88	100%

TABLE 4
TEMPORAL LOBECTOMY
JULY 1948 TO MARCH 1965
Operative Morbidity and Mortality

A. Transitory (8 patients)	
1. Aseptic meningitis	2
2. Infected hematoma	2
3. Hypersomnolence	1
4. Oculomotor palsy	1
5. Manifpulation hemiplegia	1
6. Aphasia	1
B. Permanent (8 patients)	
1. Upper quadrant field defect	6
2. Hemiplegia and hemianopsia	1
3. Hemorrhage, massive pulmonary edema, death (1.3%)	1

TABLE 5
TEMPORAL LOBECTOMY
JULY 1948 TO MARCH 1965
Summary of Causes of Death

Recurrent neoplasm	10
Suicide	2
Basal skull fracture	
a) due to convulsions	1
b) due to accident	1
Operative complications (1.02%)	1
Pulmonary tuberculosis	1
Cardiac failure	1
Chickenpox Encephalitis	1
Total patients	18

arteriography are usually performed in order to establish the pathologic basis for the seizures if the clinical seizure pattern and serial electroencephalographic studies suggest localization of the epileptogenic area. Isotope studies and echoencephalography are usually not helpful in localizing chronic epileptogenic lesions, in our experience.

4—Electroencephalographic (EEG) Examinations

Serial electroencephalography is obtained to localize a cortical epileptogenic area in one temporal lobe, if possible. Recordings during drowsiness and sleep (or activation by Metrazol) with international electrode placements and additional electrodes in the anterior temporal areas bilaterally, have proved to be the method of choice. Sphenoidal electrode placements are frequently useful. We have had less success with nasopharyngeal leads. Stereotactically implanted electrodes have been reported to offer additional assistance in EEG localization by Crandall, Walter and Rand[8,9] in patients who have bitemporal EEG focal abnormalities. We are reluctant to implant electrodes in both hippocampal areas in an attempt to lateralize the epileptogenic area in patients who seem to have bitemporal epileptogenic foci because a) our present EEG techniques have been satisfactory, b) the possibility or probability exists that the epileptogenic area is too diffused to respond to local surgical excision due to its subcortical, limbic or reticular involvement, and c) the theoretical possibility is present of creating epileptogenic areas in previously quiescent and strategic structures. Intracarotid sodium amytal tests[10] will confirm the side of the brain harboring speech and occasionally will provide information concerning the propagation of discharges from an epileptogenic area. It should be emphasized that EEG foci shift and sometimes disappear with maturation of the brain. It is for this reason that young children must be studied most carefully before surgery is decided upon.

5—Anticonvulsant Medical Treatment

Intensive and methodical treatment with anticonvulsant drugs must be demonstrated to be inadequate to stop the seizures or to assist the patient with normal home, school or job adjustment. The ultimate goal of the care of the patient is acceptable social and economic rehabilitation. It is usually found that by

TABLE 6
TEMPORAL LOBECTOMY—July 1948 to March 1965
Control of Seizures—Seventy Patients

	Number	%
No seizures, aurae, medications	7	Acceptable results in 50 or 71.4%
No seizures, aurae but on medications	16	
Acceptable reduction of seizures, aurae and medication (a) Aurae only (5) (b) Less than 3 seizures since surgery (15) (c) Less than 6 seizures annually (7)	27	
No significant change	20	Unacceptable results in 20 or 28.6%
Aggravation of seizures	0	
Total	70	100%

the time the patient is referrred to the neurosurgeon everyone concerned has lost confidence in drug therapy and surgery is considered because of this.

In summary, the selection of epileptic patients for temporal lobectomy is made following consideration of factors depicted in Table 1.

Analysis of Temporal Lobe Surgery (1948-1965)

The following nine tables provide a summary analysis of our experience with limited temporal lobectomy for selected patients with unmanageable psychomotor epilepsy. This study includes consideration of etiological factors as suggested by history and examinations (Table 2), surgical pathology (Table 3), operative morbidity and mortality (Table 4), summary of causes of death (Table 5), control of seizures (Table 6), psychotic patients (Table 7), social and economic rehabilitation (Table 8), clinicopathologic correlation of results (Table 9) and comparison of results in our previously reported 1948-1961 experiences with those between 1961-1965 (Table 10). □

CONCLUSIONS

1. Accurate diagnosis is required in the study of each epileptic patient. Instead of an arbitrary classification with either purely descriptive or anatomical terminology, it is preferable to combine all possible sources of information. Thus, the character of the seizure pattern is best defined in descriptive terms, (i.e., psychomotor epilepsy), but this should be supplemented by anatomical location of the epileptogenic area (temporal lobe, frontal lobe, insula or subcortical area), and the underlying pathology (inferomesial temporal sclerosis, neoplasm, vascular malformation or hamartoma).

TABLE 7
TEMPORAL LOBECTOMY
July 1948 to March 1965
Psychomotor Epilepsy and Psychotic Behavior

Patients	Pathology	Dependent	Dead	Independent
8	Obscure	3	4	1
3	Inferomesial sclerosis	0	0	3
3	Other atropic lesions	2	0	1
0	Neoplasms	0	0	0
14		5	4	5

TABLE 8
TEMPORAL LOBECTOMY—July 1948 to March 1965
Social and Economic Rehabilitation

Status	Before Surgery	After Surgery	
Dependent and non-productive	70	18	25.7%
Partially self-supporting	0	9	8.3%
Independent, productive and self-supporting	0	43	66%
Total	70	70	100%

TABLE 9
TEMPORAL LOBECTOMY—July 1948 to March 1965
Clinico-pathologic Correlation of Results

Pathology	Patients	Dependent	Dead	Independent
Chronic atrophic lesions Infero-mesial sclerosis	44	9	2	33
Meningo-cortical cicatrices	15	7	3	5
Neoplasms	15	2	10	3
Obscure	14	10	3	1
Total	88	28	18	42

TABLE 10
TEMPORAL LOBECTOMY—July 1948 to March 1965
Comparison of Results

Period	Patients	Pathology	Dead	Dependent	Independent
1948-61	78				
	36	Mesial Temporal Sclerosis	2	8	26
	14	Cicatrices	3	6	5
	14	Neoplasms	10	2	2
	14	Obscure Causes	3	10	1
1961-65	10				
	8	Mesial Temporal Sclerosis	0	1	7
	1	Cicatrix	0	1	0
	1	Neoplasm	0	0	1
	0	Obscure	0	0	0
	88		18	28	42

2. The success of the operation depends on the care with which the patients are selected, the operation itself and the after care.

3. Psychiatric abnormality, including psychotic behavior of long standing, may be reversed sufficiently in some patients with psychomotor epilepsy to provide satisfactory social and economic rehabilitation, provided the epileptogenic area is excised and deterioration of personality is not advanced.

4. Because of the relatively high incidence of organic pathology, particularly neoplasms (10 to 20% in various reports), each epileptic patient deserves thorough study.

5. Mesial temporal sclerosis, involving the anterior portion of the hippocampal gyrus, amygdala and hippocampus, due to a variety of causes is the most common cause of a focal epileptogenic area of the brain and the most satisfactory lesion to treat surgically from the standpoint of control of seizures and social and economic rehabilitation. □

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□

THE IMMUNOLOGIC DIAGNOSIS OF PREGNANCY

Richard Carter[1]
William Landau, Ph.D.[2]

INTRODUCTION

Until recent years the laboratory's only contribution to the physician's diagnosis of early pregnancy involved the use of animals as indicators of the biologic effects of human chorionic gonadotropin (HCG). The rat, mouse, toad, frog, and rabbit have all been employed successfully for many years and are well accepted by both the physician and the laboratory alike. Each of the animal indicators has an accuracy of about ninety percent or better and is often a necessary aid to the clinical evaluation. However, the use of animals has certain inherent disadvantages: biologic and seasonal variation of animals, death of animals due to toxic urine, the cost of purchasing and maintaining an animal colony and the length of time required to obtain results.

For the past few years several new types of tests have been reported, all of which are based on the antigenic rather than the biologic activity of HCG.[1,6] Such tests do not require the use of animals, they yield results much more rapidly and if shown to be as accurate as an animal test, would be most desirable.

Several immunologic tests have been evaluated in comparison with various animal tests and found to be as accurate or more accurate than the traditional methods. We wished to make such an evaluation for ourselves to see if, in our own hands, an immunologic test could safely replace the Friedman rabbit test ordinarily used. Such an evaluation is the subject of this report.

MATERIALS AND METHODS

Urines

Urines routinely submitted to the laboratory for pregnancy tests were used. They were evaluated immediately by immunologic tests and then refrigerated for later use in the Friedman Test.

HCG Standard

The international human chorionic gonadotropic (HCG) standard prepared by the National Institute for Medical Research, Mill Hill, London, England, was used to determine the sensitivity of the pregnancy tests used in this study. The standard was diluted to various concentrations in phosphate buffered saline (pH 7.34) and was kept frozen at —65°C. Small aliquots were thawed just prior to use and the portion not used was discarded after each experiment.

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[1]Research Assistant, Department of Microbiology, Presbyterian-St. Luke's Hospital during summer of 1965.

[2]Associate Director, Department of Microbiology, Presbyterian-St. Luke's Hospital; Instructor of Microbiology, University of Illinois College of Medicine.

TABLE I
Sensitivity of two immunological pregnancy test systems

HCG Concentration (I. U. per ml.)	Gravindex			UCG (Standards diluted 1:3)		
	Positive	Doubtful	Negative	Positive	Doubtful	Negative
10	9*	0	0	6	3	0
7†	—	—	—	1	1	0
6	11	0	0	1	5	3
5	11	0	0	0	6	5
4	2	0	12	—	—	—
3	0	0	12	—	—	—

*Number of Determinations.

†7 I. U. per ml was taken as the threshold level for the UCG test since there were no negative tests at this concentration and, as prescribed, the repeat of doubtfuls, undiluted gave positive tests.

Immunologic Pregnancy Tests

All the currently used immunologic pregnancy tests are based on agglutination-inhibition reactions using antiserum to HCG, latex particles or stabilized red cells coated with HCG and the urine to be examined for the presence of HCG. Urine and antiserum to HCG are mixed on a glass slide or in a test tube after which HCG coated latex particles or red cells are added, mixed and examined for agglutination after a brief 2 minute reaction period for slide tests (latex particles) or 1 to 2 hours for tube agglutination tests (stabilized red cells). If the urine contains no HCG (not pregnant) the HCG antibodies in the serum remain free to agglutinate the antigen coated carrier particles (negative test) and conversely if HCG is present in the urine (pregnant) it combines with the antibody which is then no longer free to agglutinate the antigen coated carrier particles leaving them in uniform suspension (positive test).

The immunologic pregnancy tests used in this study were the latex slide agglutination and the UCG stabilized red cell hemagglutination tests.* The tests were conducted exactly as prescribed in the literature accompanying the commercial test kits. All reagents were kept refrigerated and care was always taken to allow the antiserum to warm to room temperature before use.

Friedman Test

Virgin female rabbits weighing between 1500 and 1700 grams were used for the Friedman Test. Ten milliliters of urine were injected on each of 2 successive days and the rabbits were sacrificed on the day following the 2nd injection and examined for the presence of corpora hemorrhagica.

RESULTS

Table I summarizes the results of the Gravindex and UCG tests performed with prepared HCG standards. It can be seen that the Gravindex test became positive at a hormone concentration of 4 to 5 international units per milliliter (I.U./ml) and the UCG test at about 7 I.U./ml. (Since this test is ordinarily run at a 1:3 dilution of urine, it is actually measuring 2.3 I.U./ml). Therefore, if the HCG concentration in a urine specimen is the same as, or greater than these threshold levels, the respective immunologic method should yield a positive result. When rabbits were tested with these HCG standards we found positive results

*Gravindex, Ortho Pharmaceutical Corporation, Raritan, N. J. and UCG, Wampole Laboratories, Stamford, Conn.

TABLE II
Comparison of results of an immunological and a biological pregnancy test

	Gravindex	%	Friedman Test	%
Total Correct	222	96.9	221	98.6
False Positives	4	1.8	2	0.9
False Negatives	3	1.3	1	0.45
Total Tests	229		224*	

*Five Friedman tests were inconclusive because the rabbits died due to toxic urines. Repeat specimens were not submitted.

with an HCG concentration of about 0.65 to 1.0 I.U./ml when a total volume of 20 milliliters was injected on two successive days. Since we found the Gravindex test to be slightly more sensitive than the UCG test and since with the former, results can be obtained in a few minutes instead of 1 to 2 hours required for the UCG test, we compared the Gravindex immunologic test with the Friedman biologic test on all urine specimens we received for routine pregnancy tests over the next several months.

A total of 229 urines have been compared by the two test systems and the accuracy of the results were confirmed by the attending physician (Table 2). Results of both tests agreed in 214 out of 224 urines (75 positives and 139 negatives). In addition, both tests gave identical results with 75 urines obtained from women on whom we could not obtain any clinical information.

Limited tests on the stability of HCG activity in the immunologic test system showed that filtered, sterile solutions containing only threshold levels of HCG could be stored for 4 days at 4° or 37°C. These findings are in agreement with the data presented by Noto and Miale although we cannot agree with the significance they attach to occasional slight losses of activity.[8] From our data and theirs it is clear that the antigenic activity of HCG is stable for at least 4 days even at a storage temperature of 37°C.

COMMENTS

We have compared an immunologic pregnancy test (Gravindex) with the Friedman test and found each to be about 97% to 98% accurate. Although the results indicate that the Gravindex test may yield a few more false results (both positive and negative) than the rabbit on routine urine specimens, the numbers are too few to be of significance. Obviously, a false negative may be observed in either test if the HCG level is too low to be detected at the time the specimen was taken and in addition, with the immunologic tests if the antiserum is not allowed to reach room temperature before the test is performed. A false positive with the Gravindex may be observed if the HCG antiserum used in the test has deteriorated due to improper storage or if the specimen contains unspecific agglutination inhibitors. In absolute terms, a minimum of 13 to 20 I.U. of HCG are needed for a positive Friedman test (20 ml of urine containing 0.65 to 1.0 I.U. HCG/ml) and only 0.25 I.U. HCG for a positive immunologic test (one drop of urine containing 4 to 5 I.U. HCG/ml). These values are in general agreement with results reported from other laboratories.[6,7] It would appear that the Friedman test is more sensitive (threshold 0.65 to 1.0 I.U. HCG/ml of urine) than the immunologic tests used in this study (threshold 4 to 7 I.U. HCG/ml of urine). But the difference in sensitivity is of minor importance for the laboratory diagnosis of pregnancy, because the curve of HCG concentration in the urine rises so steeply in the early phases of pregnancy that the variation in threshold levels of the various tests would at most make a difference of one

to three days in terms of the earliest date a positive laboratory diagnosis could be made. On the other hand, the immunologic test system can be accurately quantitated and is independent of variations inherent in any biologic test system, i.e. variations between individual test animals and seasonal variations of animals in general. In addition, the difference in ease, speed and cost of the two different test systems needs no further emphasis, particularly since the immunologic test systems can also be used for quantitative tests with great accuracy.

Quantitative tests, for example, may be used for studying women with repeated habitual abortions or patients with hormone-producing tumors. Noto, Miale and Riekers[7] found that a positive immunologic test with a titer of 1:64 (320 I.U. per ml) was compatible with normal pregnancy during the first trimester but at levels of 1:128 (640 I.U. per ml) or above, there is indication of pathology such as chorioepithelioma. They recognize the fact that their data are limited and caution against placing emphasis on a titer without careful clinical-pathologic correlation. But, in their experience, there was closer agreement between the clinical history and the quantitative immunologic test than with the quantitative biologic test. □

SUMMARY

1. The threshold of sensitivity of three pregnancy tests has been found to be: Gravindex, 4 to 5 I.U. per ml; UCG, 7 I.U. per ml; Friedman rabbit test, 0.65 to 1.9 I.U. per ml.

2. An immunologic slide test for pregnancy (Gravindex) has been compared with the Friedman rabbit test using 229 urine specimens. The results obtained were essentially the same with both tests, showing 97–98% accuracy.

3. When a quantitative test is required to differentiate certain pathologic states from normal pregnancy, the greater ease and speed of the immunologic test are distinct advantages. □

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RECONSTRUCTIVE VASCULAR SURGERY BY ENDARTERECTOMY*

João Cid dos Santos, M.D.[1]

INTRODUCTION

The address which follows was not a formal paper read by the dynamic Portuguese surgeon, João Cid dos Santos (Figure 1), but one of the many informal talks which he gave in some of the teaching centers throughout the city of Chicago. He was unaware that his talk was being recorded on tape and some of his remarks may have been misinterpreted. Nevertheless, the impact of this fertile, restless genius, mellowed by extensive contact with surgeons in Europe and throughout the world is here recorded—an idea polished and perfected by its originator who created, by pure accident and considerable serendipity, a method which is here to stay.

The record of the early failures, the tenacious search for improvement and the efforts to eliminate causes of failure are of great historical interest. The reference to Tuffier's rubber glove which he sewed into an aneurysm should cause everyone to rush to the dramatic description in the original (Bulletins et Mémoires de la Société Médicale des Hôpitaux de Paris, 1909). Or are you late now for the next meeting?

Geza deTakats, M.D.

While we hear that certain procedures have solved the problem of direct surgical repair of chronic vascular diseases, we still find that opinions vary and we may reach the conclusion that this problem is not solved at all. Current surgical procedures employed in chronic arterial diseases should be compared with each other, but such comparisons should take place only after sufficient cases have accumulated and probably there will never be a "best" one. Rather, several methods might be utilized at the same time. We often forget when we speak about endarterectomy that this type of surgery is different from every other because it is probably the only surgery where one works directly with diseased tissue. Endarterectomy, of course, is only one of

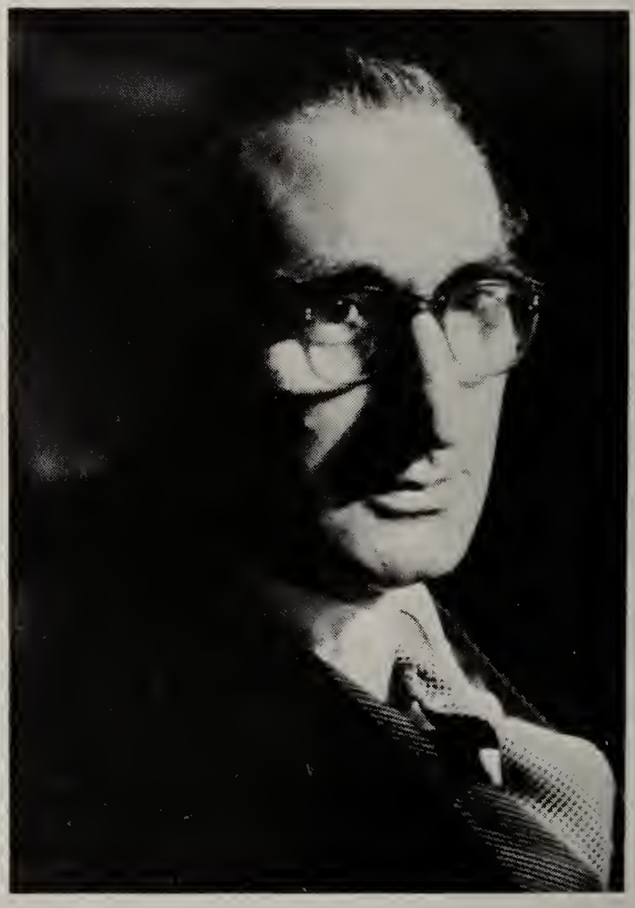

Fig 1.—Dr. João Cid dos Santos, Professor of Surgery, University of Lisbon.

*Presented as a Special Lecture to the Division of Surgery, Presbyterian-St. Luke's Hospital on September 19, 1965.

[1]Professor and Director, Department of Surgery, University of Lisbon, Lisbon, Portugal.

the methods that can be used, and if I use it nearly exclusively, it is not because I find it better or worse than the others, but because I wanted to pursue it to the extent of its limitations.

I do not know what the final result will be, but the biological meaning of the operation is that blood can pass along denuded muscular tissue without thrombosis and that a new endothelium can form. The operation probably marks a step and this step ends a "myth". . . the myth of the endothelium . . . the myth in which we have all been trained; namely, that you should never touch the lining of an artery, and that you should have an intact arterial lining since without it thrombosis will follow every arterial operation. I feel strongly that even if endarterectomy is not used in later years, at least this principle will never be lost. It is an end to the notion of the need for the integrity of the intimal lining. Of course, it also has interesting applications to other aspects of vascular surgery.

In the first experimental case, heparin was administered because I thought that if I could maintain the patient on heparin, a thrombosis would not develop and possibly a new endothelium would be produced. To try this, since it was not possible to try it in animals, I did it in a patient* who was critically ill with a high degree of atherosclerosis. In addition, he had an obliteration of the femoral artery. We had not had preoperative arteriography and instead of doing the classical operation, which was a resection of the artery as Leriche had taught us in 1935, I made, under local anesthesia, an incision in the artery and with improvised instruments removed everything that was inside. I thought it was a thrombus and yet there was none. Then I closed the vessel and had an arteriogram made on the operating table. We saw that the collaterals at the level where the obliteration had been present were functioning. This was a finding which proved to be useful later. When the pathologic report came, it showed that there was no thrombus and that all the inner lining had come out. Two or three days later when the patient died of unrelated causes, the artery was still patent.

A month later, a young woman appeared with an obliteration of her subclavian artery. I tried to open this artery, the axillary and the brachial at three levels with the same improvised instruments. The tissue plugging the artery was removed. Again, microscopic examination showed that the endothelium was also removed with it. We were pleased when this vessel remained patent. This was sheer luck, because later I discovered that what I had removed from the brachial had plugged up again, so that only the subclavian and the axillary remained patent. A very wide profunda brachialis made the collaterals work and time proved that the circulation remained in excellent condition. Originally, she had a very serious ischemia, the original cause being a scalenus anticus syndrome with an endarteritis at and below the compression together with dilatation and thrombosis. This vessel has remained patent and the good results have lasted nineteen years. This gave me courage for the ensuing years because all our other cases did rather poorly. It is interesting that I chose the worst region for the first operation, the femoral, because even today we have many doubts about this site. At that time, while using too much heparin and with ignorance of many details, we had one thrombosis or hemorrhage after another and many cases were lost. Some of these operations were technically correct but many failed for other reasons so that the final results were very poor. From time to time a favorable case would give us some hope and from this period, which extends from late 1945 until 1962, there were about 80 cases of which I have kept complete records. In this series there remained only five patients with patent arteries; two were done the first year in the common femoral and subclavian; another one with a twelve year follow up; the fourth with a six year follow up; and the fifth in the

*This was the first endarterectomy in the world. *Editor.*

aorta with a five year follow up. I could never obtain the figures prevailing in your country, but I know that Wiley was the first to perform endarterectomies in the aorta with much better results than I was obtaining at that time. My results being as poor as they were, I thought that I would have to add some refinements to the procedures.

The Patch

The first of my refinements was the patch. This was the patch that DeBakey derived from the old studies of Carrel, who really did the first patch. It is curious, because only a very few people know that Carrel not only did the first patch with autologous tissue, but he did the first artificial patch with rubber which had been suggested by Tuffier. Tuffier was operating on a descending aortic aneurysm in 1909 and since he had no other tissue with which to repair the defect, he slipped off his glove and sutured the glove into the defect. We have the slides of that first artificial patch. Then he wrote Carrel saying that a patch of rubber ought to be tried. The rubber patch functioned for one year, and then he removed it.

The Long Patch

The second step was the long patch of Sterling Edwards. This patch is most important because it can change the caliber of the artery. In the first few cases, the caliber was not sufficient; the patch was pitted against the stenosis. The next difficulty was that the endothelium at the distal end was very thick and the current of blood dissected underneath it. My friend, Kunlin, who is the originator of the venous bypass, told me to be sure to fix this intima to the underlying tissue with a few stitches. I call them the "Kunlin stitches" and these are used to fix the intima to the edge of the distal vessel. This suturing is not easy because it is in a small, narrow place and sometimes cuts straight through the vessel. I thought that when the long patch was used, the edge of it should go further distally than the edge of the

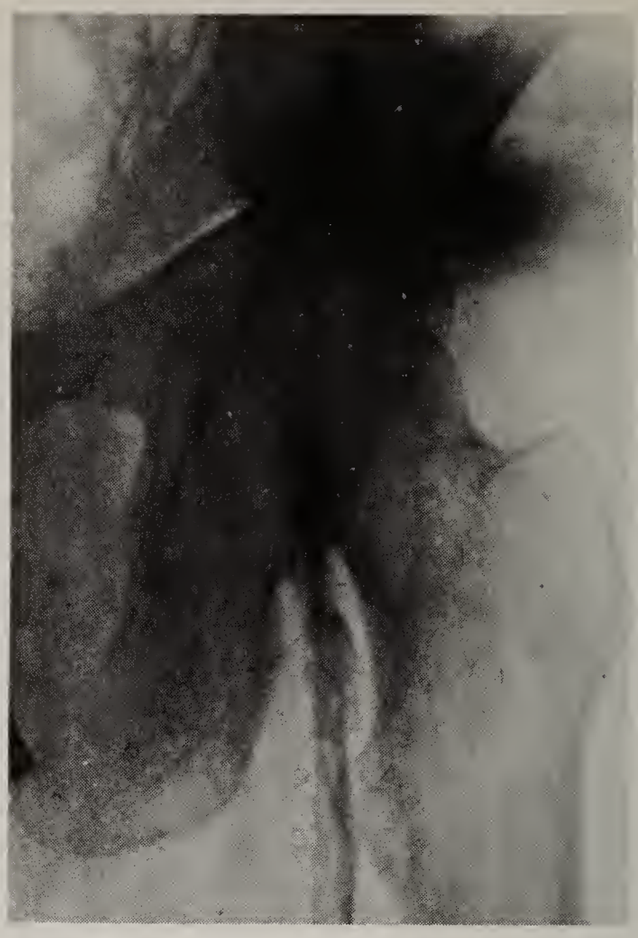

Fig. 2.—Post-operative arteriogram of elderly man with nephrosclerosis. Note: patency partially restored.

Fig. 3.—Arteriogram showing patency of the patch.

intima. We could then cut the endothelial lining much farther down and expose it with the distal end opened widely in front, thus facilitating the placing of the stitches. I thought that this was a wonderful idea of my own, and of course, as so frequently happens, someone else had also thought of it. . . . Dr. Otto H. Trippel described exactly the same thing.

To illustrate some of the problems thus far, Figure 2 is the post-operative arteriogram of the first case. This patient was an elderly man with nephrosclerosis and you note that the arterial lumens are no longer obliterated. One can see that collaterals are present, collaterals at the level where the obliteration existed. Figure 3 is an arteriogram taken on the autopsy table in which one can see that patency is still maintained.

Figures 4 and 5 illustrate our second case. Figure 4 is the drawing of the obstruction showing the levels where it was opened: the axillary, the subclavian and the brachial. Figure 5 is a post-operative arteriogram of a vessel which

Fig. 4.—A drawing of the obstruction showing levels where it was opened: the axillary, the subclavian and the brachial.

was previously obliterated. It was endarterectomized and you see the patent, deep brachial artery. This is the reason it works so well even today. This was the first demonstration that the collaterals can work at the level of endarterectomy. This patient has been well for nineteen years and the pulsations in her two hands are perfectly adequate and equal.

We now come to the examples of the first period where we had a large number of failures. Figure 6 shows what was removed from the superficial femoral artery. Figure 7 was taken post-operatively and shows two very marked stenoses; then a blockage occurred, and later a complete failure. There are several examples of many cases of failure, one of which is shown in Figure 8 from one of these operations around 1947.

Fig. 5.—Post-operative arteriogram. Profunda previously obliterated.

We then had five cases that remain patent today. Figure 9 is of the block in the common iliac artery which I operated on before the International Congress of Surgery in Lisbon twelve years ago. The patient has no post-operative x-ray because he refused to have one done, but he is in splendid shape and the pulses leave no doubt that the artery is patent.

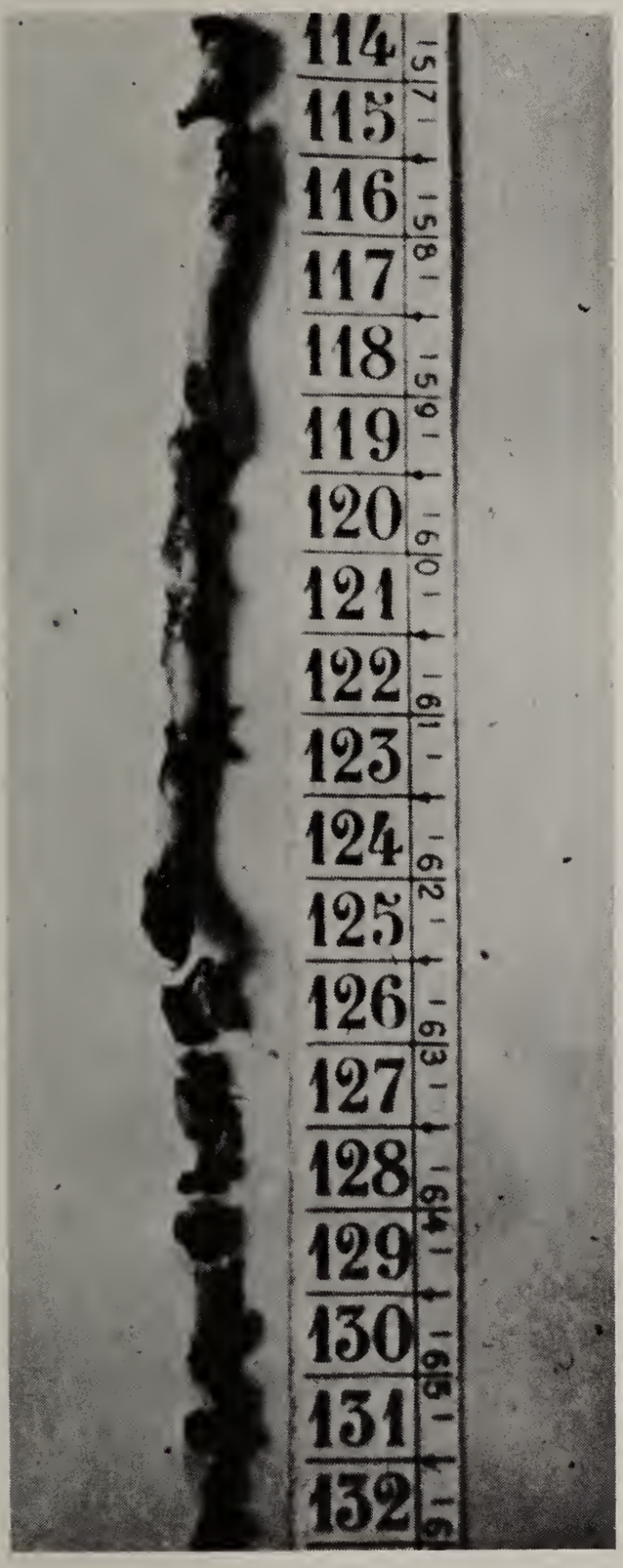

Fig. 6.—Material removed from the superficial femoral artery.

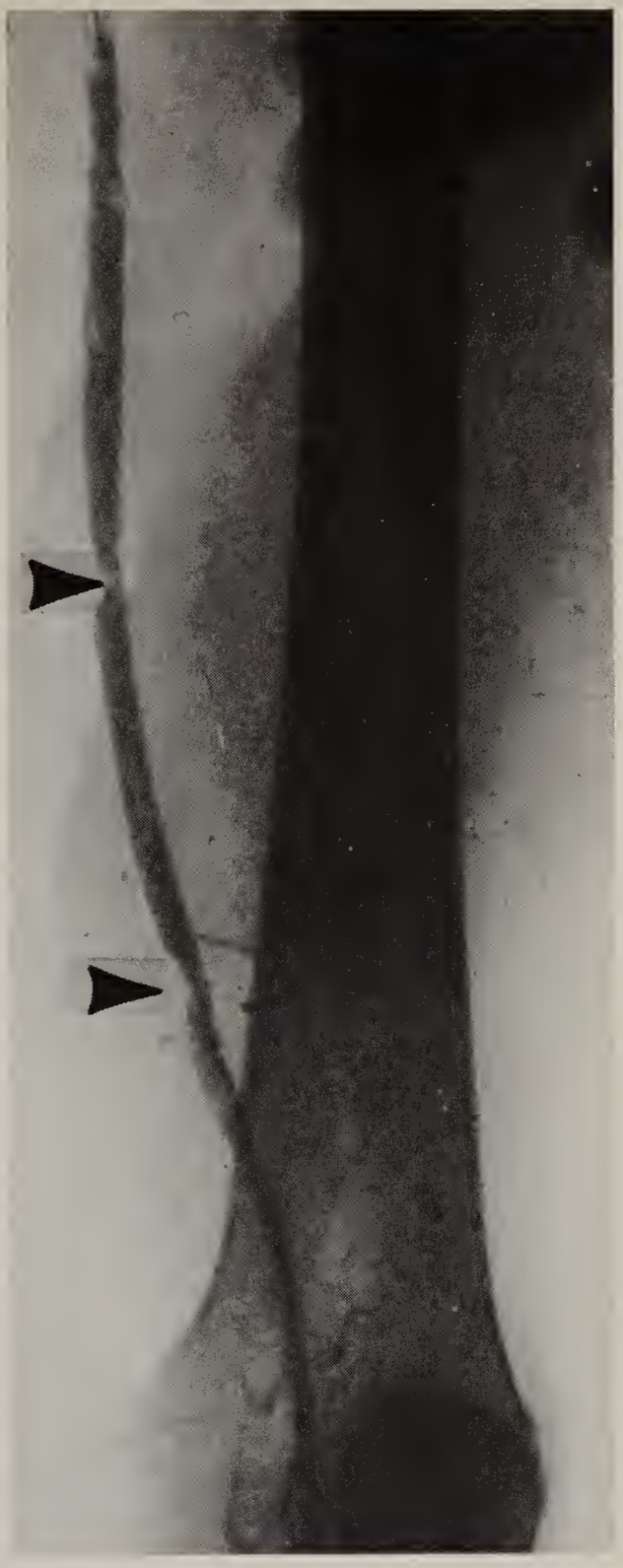

Fig. 7.—Post-operative arteriogram showing two very marked stenoses.

The next case, Figure 10, is of an endarterectomy of the left external iliofemoral segment and this is functioning today, eight years later. Figure 11 was that of a segmental occlusion of the aorta, at a level which I had never seen in the past; a localized thrombosis, which was very easily removed.

Fig. 8.—Core removed from superficial femoral artery. This vessel completely reoccluded.

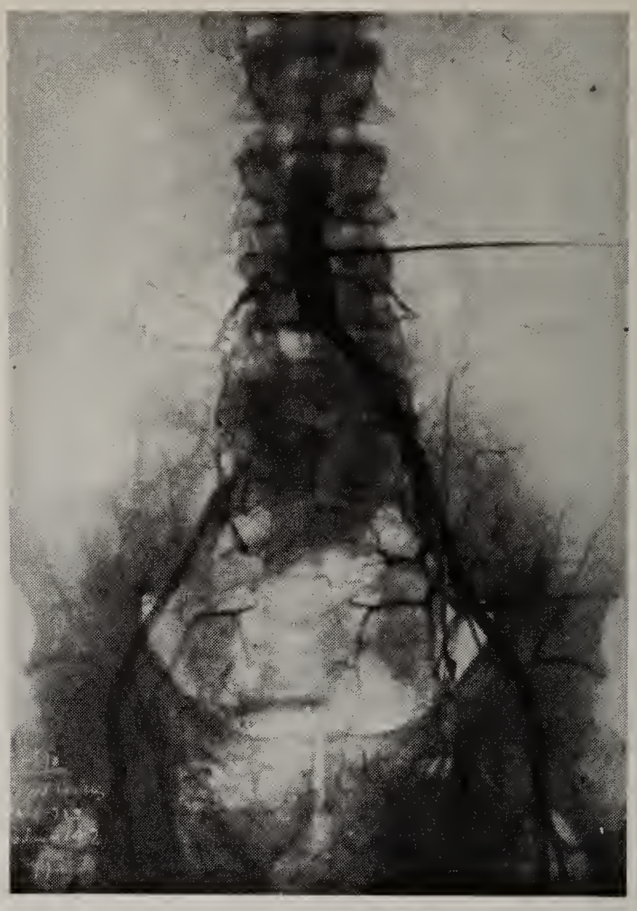

Fig. 9. Block in the common iliac artery operated on 12 years ago which remains patent today.

All of these roentgenograms are only partial ones because these pictures are only segments of a total aortoarteriography by which we mean that we start with the abdominal aorta and get pictures clear down to the feet. One particular patient had small arterial obstruction clear into the feet and this was the most localized endarteritis that I ever found. I sectioned that artery in the middle, removed the intima and the remaining plug in both directions, and sutured it end to end. He also has no x-ray control, but he is completely normal with patent pulses.

The Overpass

An operation, of course, is a series of details. You cannot depend on one simple detail. Therefore, I was able to announce a certain number of principles with which I began to have much better results. The third step, the overpass, improved my results.

When I developed the overpass idea I knew that this was perhaps the last of the three steps which made endarterectomy a much better operation than it originally was. We had originally done so-called "closed" endarterectomies where only small incisions were done both in the skin and in the artery. In Figure 12 we went over to the open endarterectomies, as was done by the French authors. You can also consider a combination of both these methods as shown

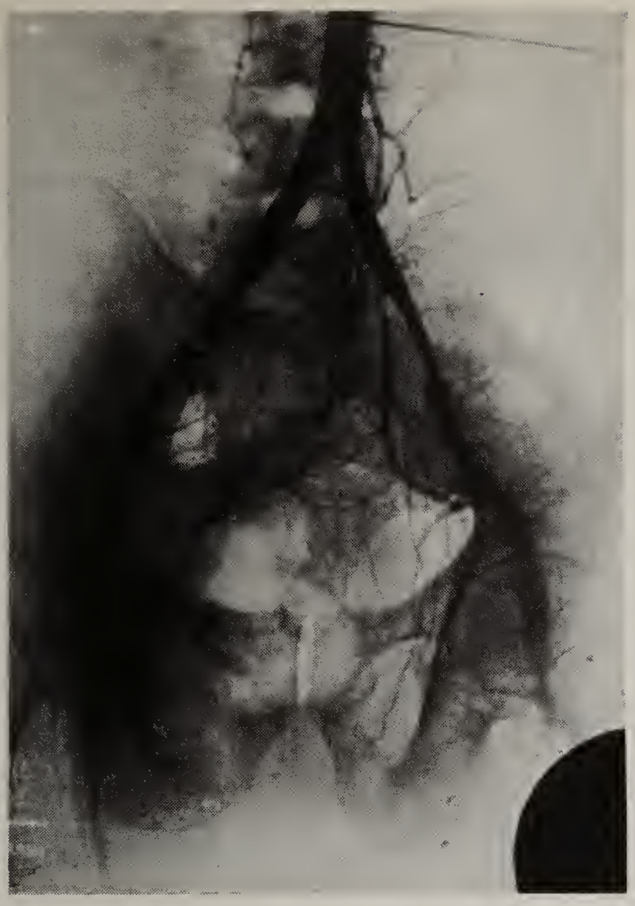

Fig. 10.—Endarterectomy of left external iliofemoral segment which is functioning today after eight years.

Fig. 11.—Segmental occlusion of the aorta, a localized thrombosis, which was easily removed.

Fig. 12.—Open endarterectomy, as done by the French authors.

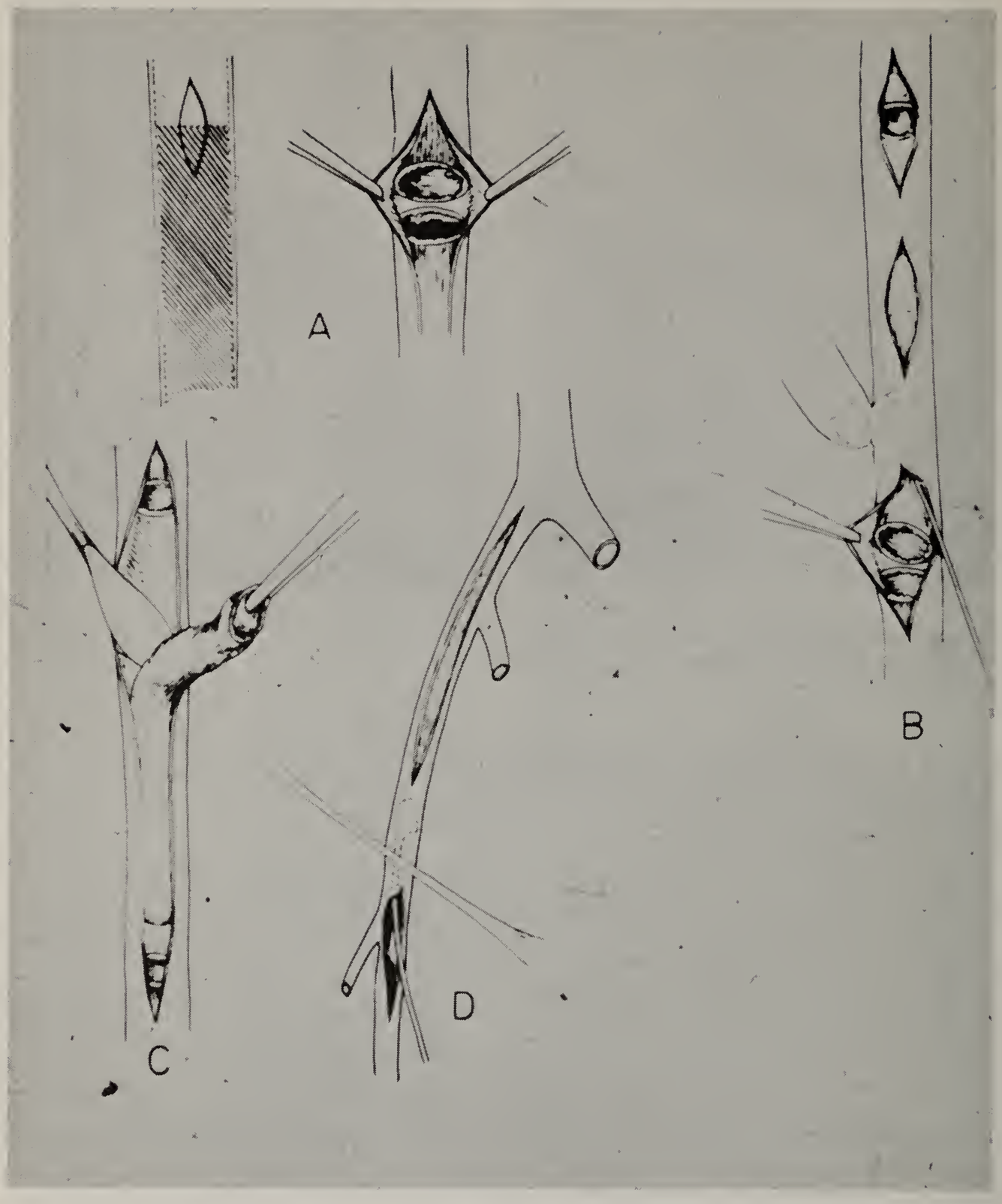

Fig. 13.—Combination of closed and open endarterectomies.

in Figure 13, where you have a closed one on top and an open endarterectomy more distally. I also feel very strongly that every endarterectomy ought to be started at the proximal end, incising the artery where it is still patent. This is important so that the upper segment does not get twisted in any way and it must be cut sharply, directly by a scissors or a knife. Sometimes I had to reoperate because of irregularities which I had left in the lining or some twisting. This is why I think you should always start at the top of the obstruction, and even above it.

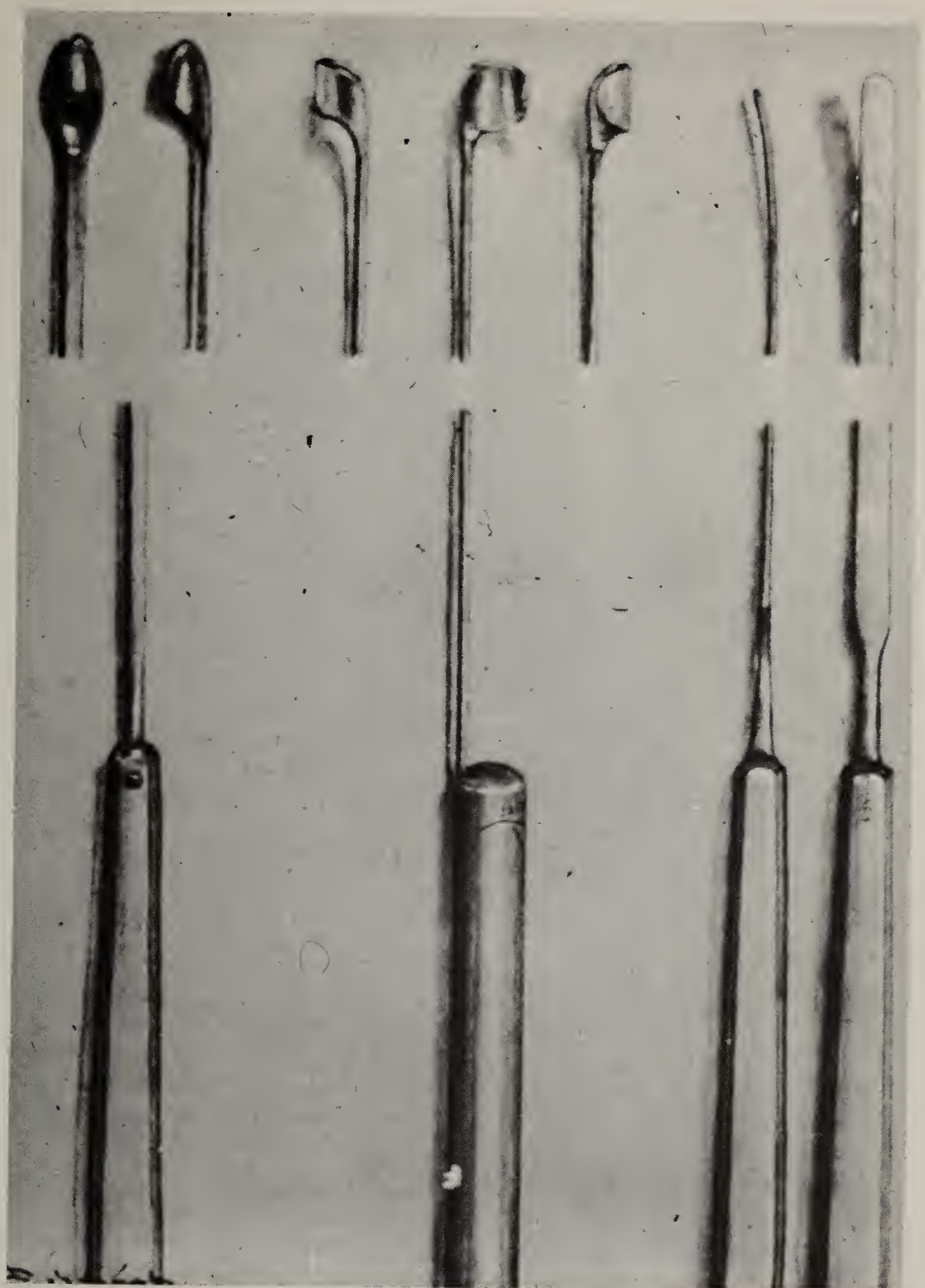

Fig. 14.—Original improvised instruments devised for long thrombectomy.

Instruments

To do the closed endarterectomy, instruments should be devised and not improvised. I had first developed a sort of spoon which I made in different sizes, some sizes that would go into the posterior tibial artery and others that would enter the common iliac or even the aorta. These were the first instruments that I devised for a long thrombectomy, before endarterectomy, because some years before endarterectomy, I had already been doing thrombectomies. These original instruments are not very good and although I have them on the instrument table they are used very rarely (Figure 14).

Figure 15 illustrates the instrument that I feel is still the best one. It is a lateral dissector and comes in many sizes since a calibre that will go into the posterior tibial will be insufficient to go into the aorta. This instrument shows also how an idea may occur simultaneously to a number of people at the same time. I had gone to the instrument manufacturer in Paris, held consultations with the chief of the department of development, and finally came to the conclusion as to how it should be constructed. At that time Kunlin, whom I have already quoted before, came into the room and saw the drawing and said "I have nothing more to do." Why was that? He had just carved one of these instruments out of wood having exactly the same idea so that we developed the same instrument simultaneously. I am still using this instrument today and it is working very well.

In this country some rings were introduced which I call "horrible rings"—and they are horrible because they do not adapt well to the differences in the size of arteries. But a few days ago, when I was visiting Otto Trippel, he asked me to watch him do an endarterectomy. When I came to the operating room, he suggested that I do it. I did it, but of course, I did not have my own instruments; I did not have my lateral dissectors, I had rings. So, I took the rings and removed the inside of the superficial femoral artery. I felt very strongly at that time that proverbs are very true. We have an old Portuguese proverb—"Never say 'I will never drink this water.' "—for that day, I drank it!

Fig. 15.—Lateral dissector simultaneously constructed by Kunlin.

Now we come to another problem, namely, that of the closed endarterectomy where we have to change the same instrument for an important reason. We did the operation originally with two or three incisions in the skin, the remainder of the artery remaining entirely covered. This should not be done because I have had to open several arteries after having destroyed the wall because I could not find a proper line of cleavage. I feel very strongly that the artery should be exposed all along its course and you should see the dissector appearing through the lumen; and then you guide it together with your finger, compressing it from the outside and from these two sides you can control the extent of your endarterectomy. This is a fundamental step in the right direction.

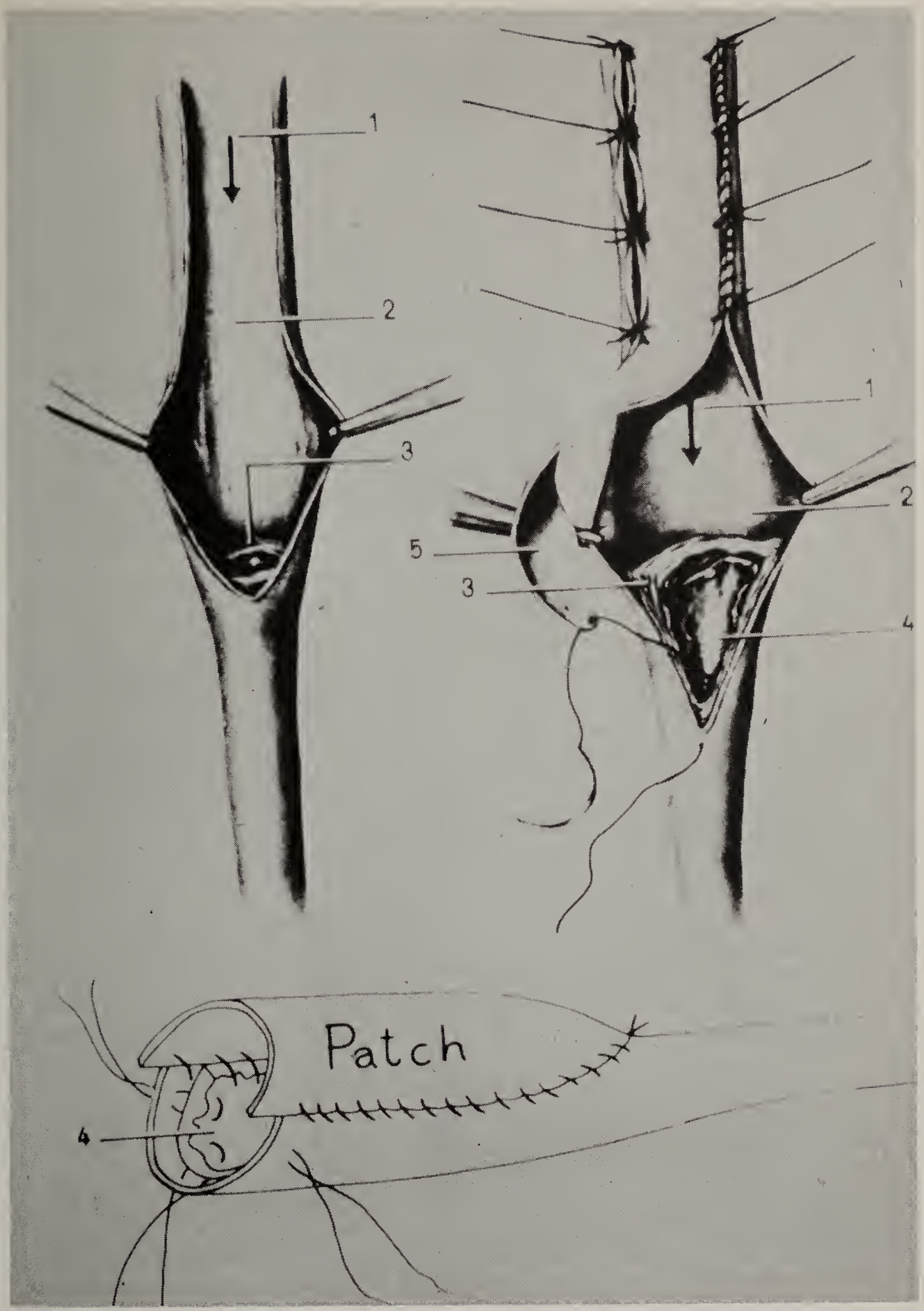

Fig. 16.—Anchoring intima on distal end of endarterectomy.

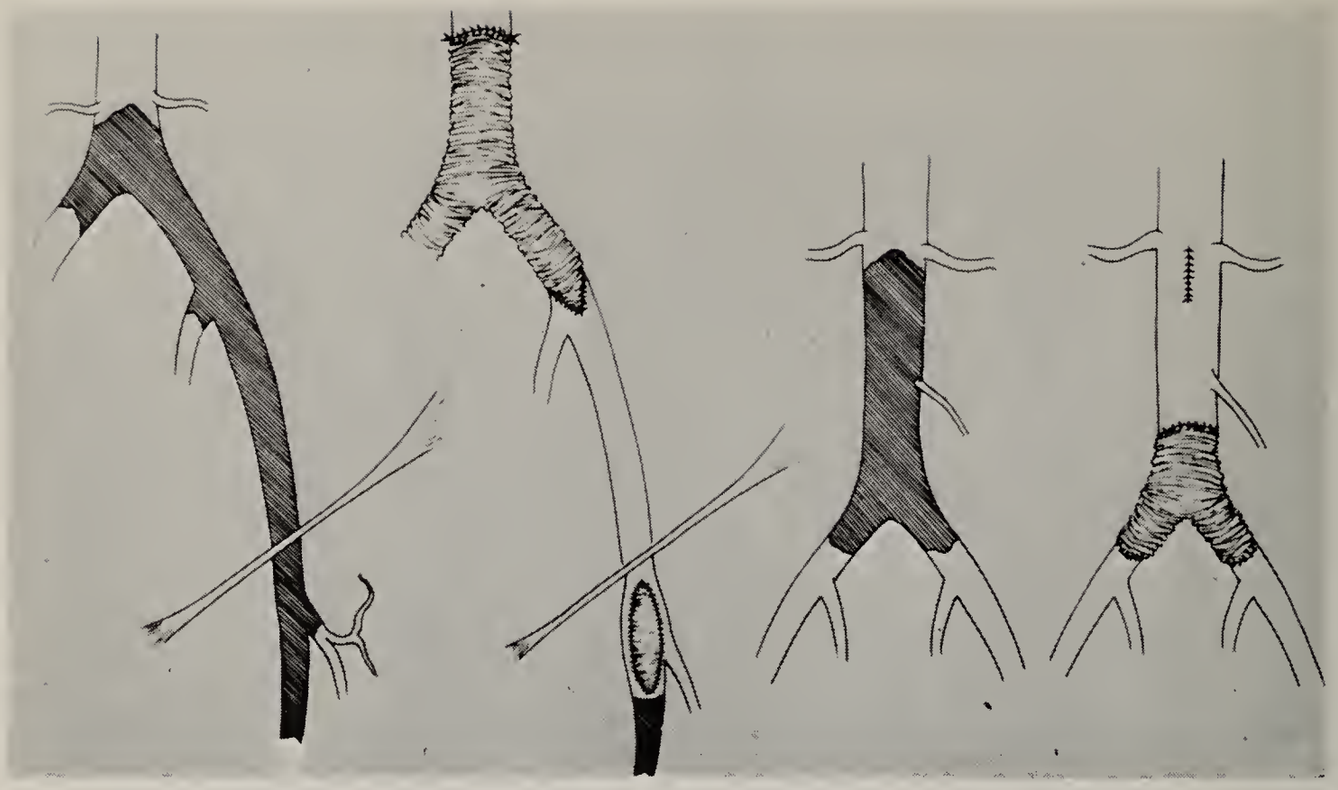

Fig. 17.—Combinations of endarterectomy with plastic prosthesis.

Then you come to the patches, the small patch; the long patch; and the combined patch; a small one and a long one; and finally to the overpass. There is a classical way of opening the vessel but it is difficult to pass stitches in the remaining intima on the distal end. But you can see in Figure 16 how easily the stitches are passed if you unroof the vessel above it; they are almost looking at you, where the patch will go. After eleven consecutive long endarterectomies of the superficial femoral artery, I only had a single failure postoperatively and this was due to a technical error. All others worked well. In Figure 17 I show two combinations of endarterectomy with an artificial prosthesis. You may have to use this combination; you may have to do an endarterectomy with a patch and then insert a plastic bifurcation. Or you may have to do an endarterectomy clear up to the renals and then put in a prosthesis lower down. These are combinations of both methods.

After these principles have been applied (I used them some 40 times), we saw an enormous difference between intra-abdominal and extra-abdominal results. First of all, among the intra-abdominal cases we had accidents, two very unfortunate ones, because we were helpless; an acute hepatitis which killed one patient and a myocardial infarct which killed another the first or second week. In both cases things were going very well in the early convalescence. We then had two other accidents which should be avoided. One patient had a hemorrhage from his iliac artery and we were too late in repairing it. Had we been a little earlier, we could have saved that man. The second complication is one of which I am very much ashamed because I do a lot of urology. I am a general surgeon, not a vascular surgeon, and I have worked all my life with the genitourinary tract. The patient had a necrosis of the ureter and an infection, and when we opened the retroperitoneal tissue some pus came out of it and the second day we saw it was urine. We were waiting for hemorrhage. It came after we had him on the table nearly dead. I

had placed a venous patch and we had to ligate the artery to remove the patch. As I was leaving the table, blood began to come from everywhere and he died on the table. How did this ureter become necrotic? The only interpretation I have is that a retractor was on it for a long time. Therefore, since then, we have always searched for the ureter and have had it widely isolated in order to avoid such a complication again.

An important type of accident was an unexpected rupture of the venous patch. I have been searching for anyone who has experienced a similar event, but nobody has told me of a rupture of the patch. This was not a rupture of a suture but the rupture of the middle of the patch by a small pinhole. The first time we explored the man, who was bleeding on the sixth day, we thought that it must have been a collateral ligature that had slipped and I passed a simple stitch and the wound remained dry. However, in the night we had to operate on another hole and the next day I had to operate on still another. The fourth time, I gave it up and removed the whole thing and put in a Dacron patch which became infected. On microscopic examination of the patch there was complete necrosis of it. In view of this, I thought the saphena magna had been too thin a vessel; perhaps it had been injured. We subsequently had portions of them examined microscopically before placing them as patches. We demonstrated that frequently there are microscopic lesions of veins that appear normal to the naked eye: calcifications, lesions of the elastic fibers, etc. I resorted to the use of the superficial femoral vein. These lesions were not caused by trauma during removal of the vein. I saw that others had removed the veins with much less care because after our first episode, we removed them with much more care, as you might imagine. The lesions must be due to the reorganization or revitalization of the patch itself. It is curious that we have had four such incidents and nobody else has had any, but things are like that in surgery. As for the future, two things may happen: I will do more patches and never have a necrosis, therefore, we will never understand the thing, or the others will begin to have them. This is the actual state of the problem and I think it is impossible to say what should be done to prevent it. □

Dr. dos Santos' presentation here comes to an end. Its content defies the usual brief summary which in any case seems superfluous. We feel fortunate in having been able to present this account of original and pioneering work told by the innovator and pioneer.

EDITOR

□

HEALTH AND MEDICAL CARE IN POVERTY AREAS OF CHICAGO

Joyce C. Lashof, M.D.[1]
Mark H. Lepper, M.D.[2]

In July, 1965 a grant was awarded by the Office of Economic Opportunity (OEO) to the Chicago Board of Health to examine present patterns of providing health care, to evaluate health needs and to plan a program to meet these needs in Chicago's poverty communities. The authors were given an opportunity to direct a study team for the Board of Health to accomplish these aims.

This report summarizes the major findings and recommendations of the study group. The Chicago Committee on Urban Opportunities (CCUO) had prepared a statistical analysis of Chicago, dividing the city into poverty and non-poverty areas. In CCUO's analysis poverty was defined as the association of the following characteristics within specific areas of the city: low income, low education, poor housing, large proportions of the population on public assistance and high unemployment and juvenile delinquency rates. On the basis of this definition of poverty, CCUO divided Chicago's 75 community areas into 24 community areas categorized as poor and hereafter referred to as poverty areas and 51 community areas which were relatively affluent, referred to subsequently as non-poverty areas.

Detailed tables were prepared for each community area of the city using vital statistics from the Board of Health including births, deaths, infant deaths, causes of deaths and incidence of reportable diseases. Comparisons were then made between the poverty and non-poverty communities.

Among the most sensitive indices of health conditions within a community is its infant mortality rate, expressed as deaths of children under 1 year of age per 1,000 live births. This rate has traditionally been used to classify communities or populations in terms of adequacy of their level of health care. The figures on mortality according to poverty and non-poverty communities, and within each, according to white and non-white are presented in Table 1. The non-white poverty community has an infant mortality of 45.5 per 1,000 live births compared to the white non-poverty community with 22.2 per 1,000 live births. Because there are a large number of perinatal deaths caused by malformations and other non-preventable conditions, the post neo-natal mortality rate—that is the number of deaths of infants who have survived their first month of life per 1,000 survivors to 28 days—is even more sensitive than the infant mortality. Thus post neo-natal mortality caused by preventable environmental stresses shows the most striking difference between the non-white poverty population and the white non-poverty population, namely 15.6 per 1,000 survivors to 28 days against 4.9 per 1,000 survivors to 28 days, a three fold increase among the non-white poverty population.

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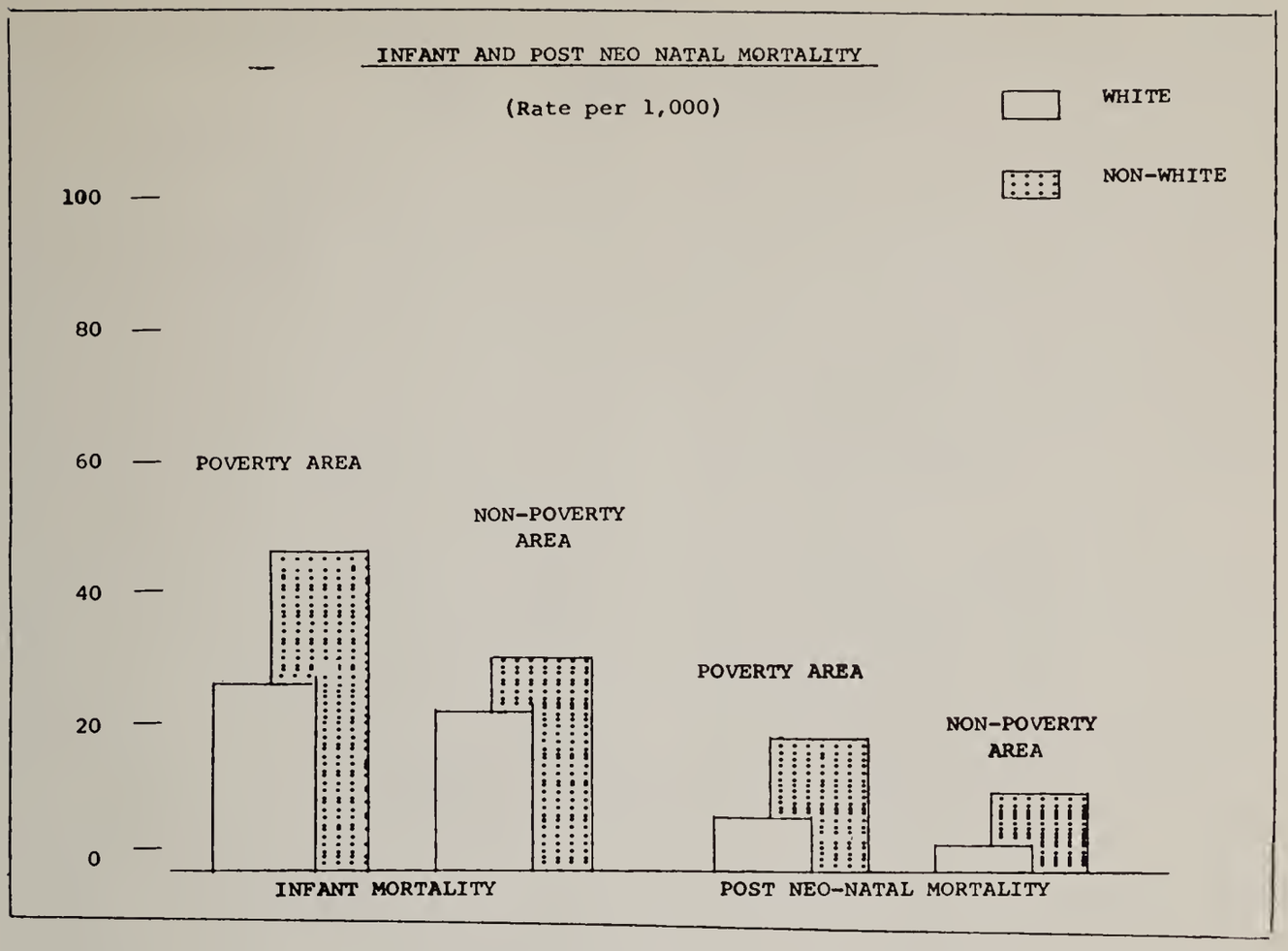
TABLE 1

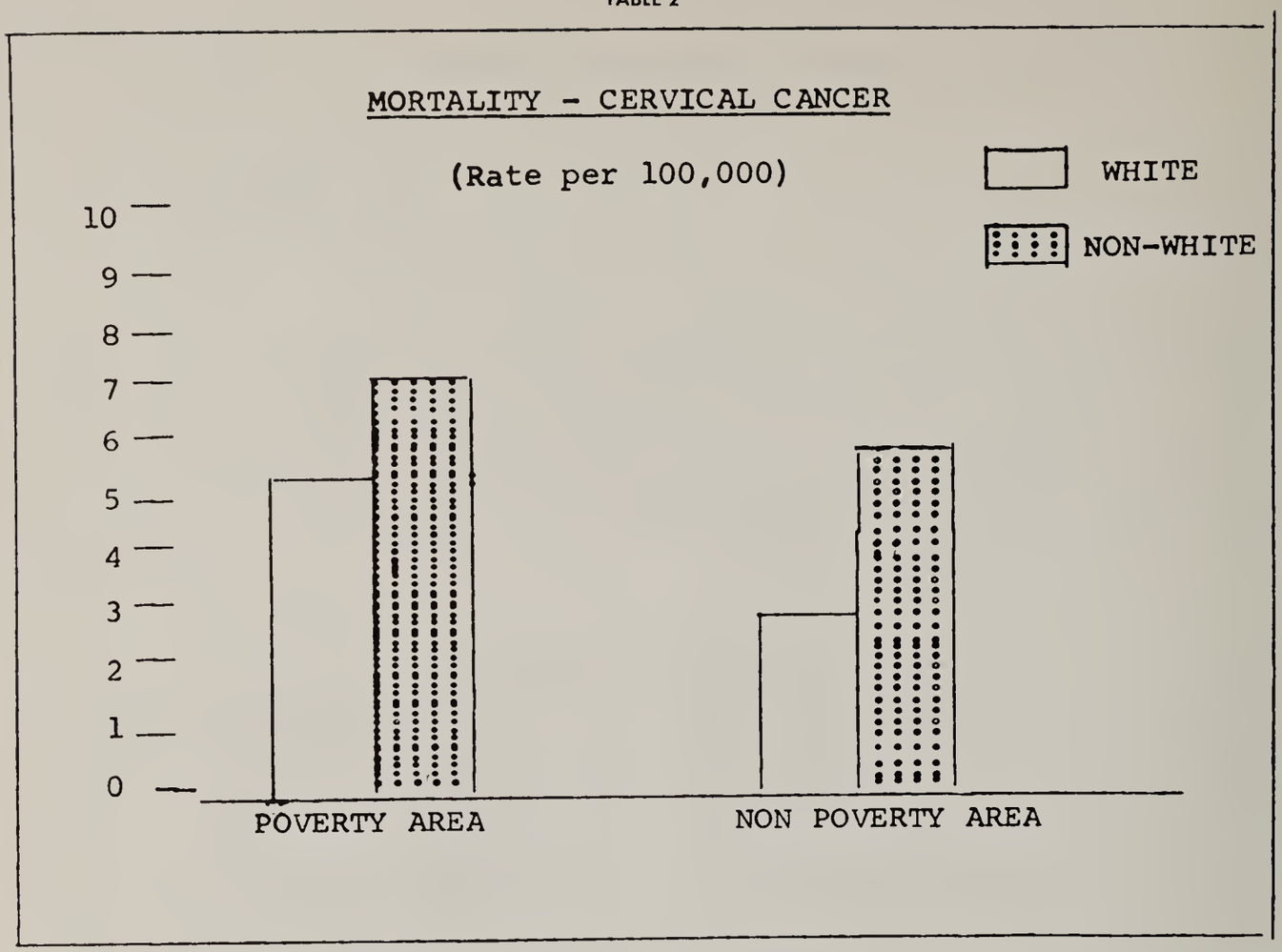


Data on general mortality is much harder to compare, because although data from death certificates for 1965 were available, the last census was in 1960 and therefore the age-specific mortality rate could not be determined. The contrast in mortality rates between the poverty and non-poverty areas was however clearly evident in data from 1960 available in the Chicago Community Fact Book. According to these data the age adjusted mortality rate in the poverty areas exceeded that in the non-poverty areas by about 40%. Data for 1965 were striking in regard to cancer of the cervix. It is generally agreed that a large proportion of all deaths of cancer of the cervix is preventable given the proper application of modern medical knowledge. The rate per 100,000 for carcinoma of the cervix is given in Table II showing a rate of 7.2 per 100,000 for the non-white poverty resident as compared to a rate of 3.2 for the white non-poverty resident.

In general the morbidity from various reportable diseases was substantially higher among the poverty than among the non-poverty population in Chicago. The data indicated that the poverty population lives at a significantly lower level of health than the population residing in the non-poverty areas. To shed light on the reasons for this, analysis of available health services was made. Evidence was found that a major discrepancy exists between the poverty and non-poverty areas as to the availability of physicians in private practice. Table III presents the figures in terms of physicians per 1,000 population. It can be seen that the supply of physicians in private practice in the poverty areas was about half of the comparable figure in the non-poverty areas. This disproportion was even somewhat more evident when the number of specialists was considered. It is true however that many members of the poverty communities turn to clinics and hospital out-patient departments for medical care.

Although it was originally the intent of the survey to obtain information on the use of physicians' services by the poverty population in order that the pattern of use might be compared with

TABLE 2



that of the non-poverty population, it proved impossible. It was possible however to obtain data from the Illinois and Cook County Department of Public Aid on the use of physicians' services by public assistance recipients in Cook County. These data were available for four federally aided programs: old age assistance (OAA), aid to the blind (AB), aid to the disabled (AD) and aid to the dependent children (ADC). Recipients under the AB program averaged about 10.4 physician visits per recipient per year, compared to 5.3 and 4.5 under the AD and OAA programs respectively. The average under the ADC however, was only 2.2 visits per recipient. The exceedingly wide range reflects the varying nature of these programs as well as a wide variation in age composition of the recipients. With regard to the latter factor, ADC recipients, for example, were mainly children and their parents or guardians, while those under OAA were, of course, considerably older. Aid to the blind recipients by nature of their reasons for needing assistance were likely to require a very large number of physician visits.

Some further light can be shed on this problem by looking at the medical payments under these four federally assisted programs as compared to the United States personal health care consumption expenditure per capita. When this comparison is made, it is found that a much higher percentage is spent for institutional care under all of the assistance programs than for the general population. The distribution of the medical dollar for institutional care, physician care and drugs is shown in Table IV. The low percentage of each dollar spent for physician care by public assistance as compared to the national average is clearly indicated. In addition data that were available from Cook County Hospital give some insight into the source of medical care for a large segment of the poverty community. Thirty per-cent of all hospital admissions from the 24 poverty areas are to Cook County Hospital. Eighty per-cent of all hospital admissions to Cook County Hospital came from 13

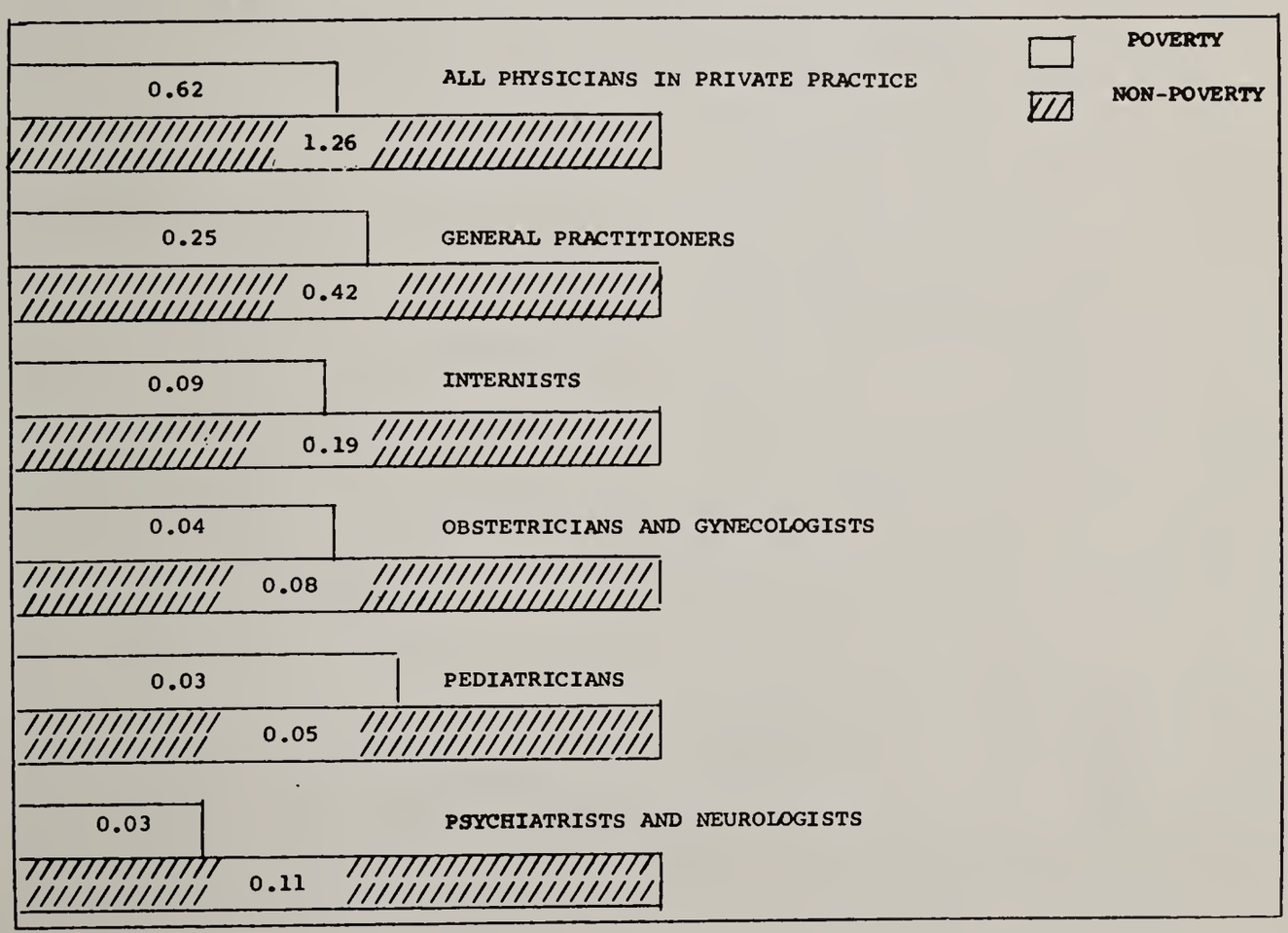
poverty areas. In surveying the patterns of medical care therefore, it is essential to know the services that Cook County Hospital provides to the poverty population. In addition to the inpatient care, there are two methods by which Cook County Hospital offers out-patient care. One is the Fantus Clinic which has general medical and various specialty clinics. Patients are accepted for care at Fantus Clinic either upon referral from the admitting and examining room services or from the hospital inpatient service for post-hospital care. Fantus Clinic was designed to handle up to 250,000 visits per year and is now past its saturation point. The anticipated number of visits for 1965 was 325,000. The hospital admitting and examining room service accounts for approximately 438,000 patient visits each year. To demonstrate how a large segment of the poverty population obtains this kind of medical care, it is worth examining the data for an average 24 hour period at Cook County Hospital. A total of 1,205 people are seen in 24 hours, 832 of whom are seen and advised. This includes 380 adults and 412 children. Forty adults were referred elsewhere. The group identified as being seen and advised required further comment. These are persons seen for a specific complaint, the complaint is handled and no provision for continuing care is made. When such a person again becomes ill, his only recourse is to appear again at the Cook County Hospital admitting service. Thus the hospital admitting room is essentially the "personal physician" for a large segment of the poverty population.

Based upon the above data an analysis of the factors of importance in comprehensive care and an evaluation of the degree to which the poverty population is receiving such care was made.

The components of comprehensive care can be defined as (1) initiation of care, (2) availability of care, (3) continuity, (4) completeness and, (5) disability limitation, which includes acute care, chronic care and rehabilitation.

TABLE 3

RATIO OF PHYSICIANS IN PRIVATE PRACTICE IN POVERTY AND NON POVERTY AREAS IN CHICAGO (Rate per 1,000 population)



INITIATION OF CARE

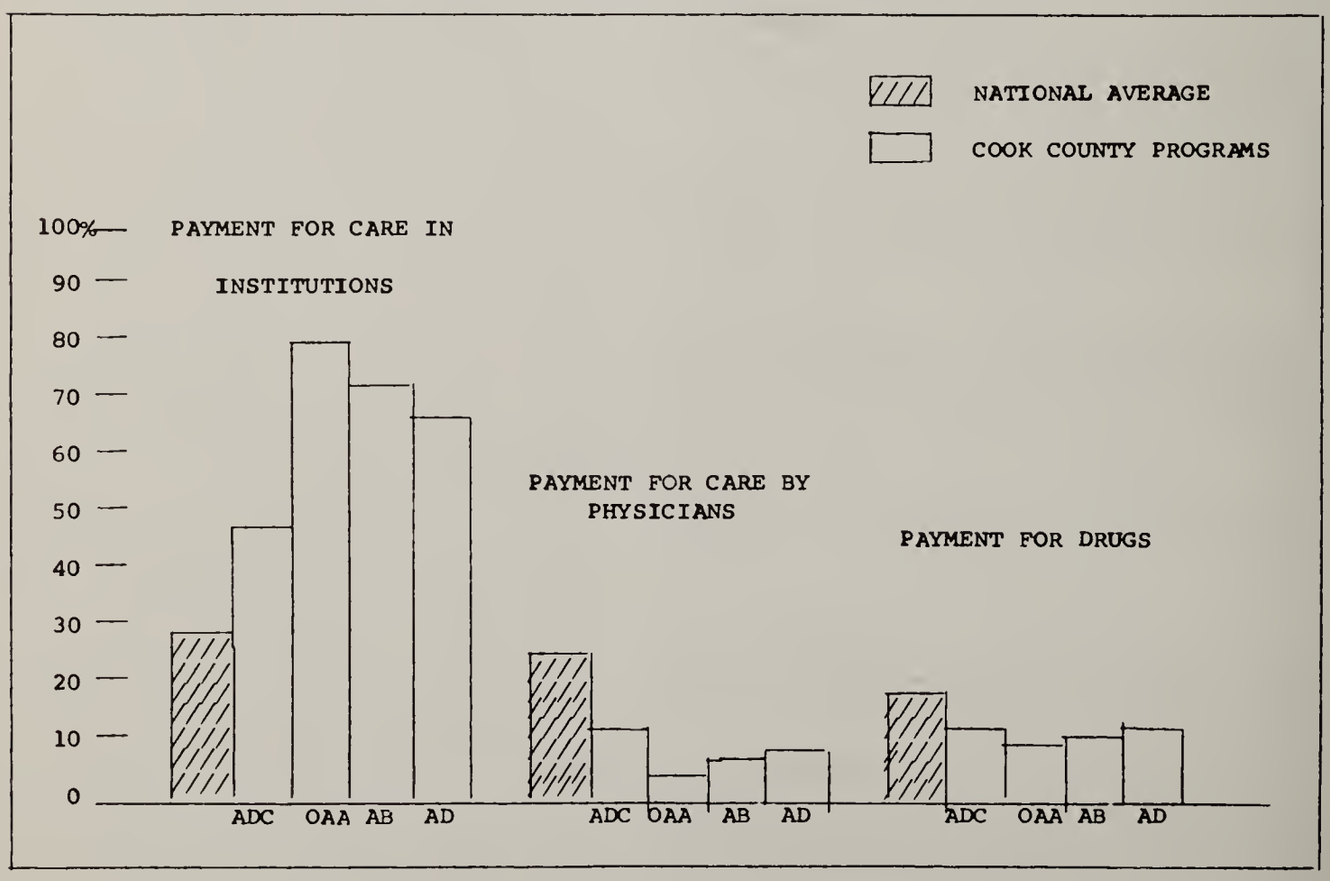
Initiation of medical care is markedly dependent upon the general educational level and cultural and emotional attitudes toward health. Appropriate utilization of the vast resources of modern medical care requires much on the part of the population. The cultural and emotional attributes of the educated and economically self sufficient segment of the population have been fairly well integrated with existing modes of health care so that basic decisions for seeking and obtaining medical care are more realistically made by this segment of the population. Although initiation of care may not be optimal for the general population, there is a marked deficiency in the ability of the under-privileged to initiate the search for aid.

AVAILABILITY OF CARE

Once the non-indigent decides he is in need of health care, it is usually initiated by use of the telephone. Despite protestations that medical care is generally not available on a 24 hour basis, the advent of answering services, group practice and emergency room availability means that the delay is generally short and the individual has the assurance that someone can be made aware of his illness and begin appropriate action. To the indigent population such services are generally much less accessible. Access to a telephone is often limited for many indigents. Moreover, access to a telephone is of little use if the indigent does not know whom to call or has no regular source of service to call upon. In dire emergencies the police may be called since they may be the only available resource. The other recourse is to travel to a hospital emergency room which is often foreign, unfriendly and terrifying to the uninitiated. However, hospitals

TABLE 4

COMPARISON BETWEEN MEDICAL PAYMENTS BY SOME COOK COUNTY PUBLIC ASSISTANCE PROGRAMS and the NATIONAL AVERAGE



have been moving away from areas of poverty in the city, and doctors' offices and clinics have become increasingly sparse in poor communities. The large charity hospital, which was once not too far by public transportation is now impossibly distant for many. In addition, the types of chronic disease now commonplace make repeated trips and visits mandatory. In this regard, the indigent is severely handicapped. It is clear that in this city the police handle most emergency transportation. This is often inappropriate and inadequate. There are generally poor transportation provisions for the person with chronic disease. Even the best public transportation, the rapid transit, usually involves the use of stairways. This places a severe limitation on its use by the old and infirm.

Having arrived at the medical care facility, there is often a long wait starting with the admission and record desk. One specific facet of this problem is that the peak load of patients seeking emergency room care is in the late afternoon and evening. This overload means that a unique and expensive staffing pattern is required. The basis for this peak is complex involving many social factors. Automobile availability through family or friend is very frequently a fundamental consideration. In addition to the patient load faced by most health care facilities, the difference in cultural backgrounds and consequent difficulty of communication between the indigent and service personnel often leads to an unfavorable therapeutic climate. Not infrequently it may interfere with or be the cause of premature termination of the medical process.

CONTINUITY

When non-poverty individuals take the initial step of seeking the services of a physician they anticipate that the appropriate decisions and arrangements for care of their illness will be made and that relatively little further initiative is needed. The persons in the poverty group cannot make this assumption. Thus, the difficulties of the poverty group in seeking and obtaining initial care are compounded in the subsequent step of obtaining appropriate referrals. For example, in the case of the non-poverty person in need of hospitalization the physician is able to call the hospital in which he has privileges and arrange for a bed, a time of admission and other appropriate orders to initiate care. The junior staff of the hospital does not have a veto power on admission of this patient. While indigent persons receive some care by private physicians, acute and emergency care is generally obtained through institutions with which there has been little or no prior contact and which are relatively impersonal to the indigent patient. Moreover the power of final decision on the question of admission of a patient to such institutions rests in the hands of its junior staff. There is no assurance that referrals from outside physicians will be admitted, regardless of the opinions of the referring physician or his advice to the patient. Similarly the non-poverty patient has access to the entire health team through consultative mechanisms which are often not as readily available to the poverty group.

Throughout the medical care system for the non-poverty patient the initiating physician is kept fully informed through active participation and generally executes control over the case. In the poverty group the referring physician rarely becomes involved in the subsequent steps of care, even if he has been successful in admitting the patient to the hospital. Once hospitalization and subsequent discharge have occurred, other factors lead to major discontinuities in the post-hospital patterns of care. Non-poverty patients usually return to the private physician's office. This doctor follows through with appropriate care plans that were begun during the course of hospitalization. In the poverty group the

outside physician, if there is one, usually is not advised without initiative on his part of the details of the hospitalization or plans for future care. Consequently, if the patient then returns to this outside physician for follow-up care, his professional service to the patient is handicapped. Moreover, it is not customary at such institutions for the patient to be returned to his outside physician, but to be assigned to its out-patient clinic, often at great inconvenience to the patient. Even within the framework of the clinic the physician rendering out-patient services frequently was not the in-patient physician and he may possess only incomplete written notes as a basis for his out-patient care of that patient.

It must be stressed that continuity of care also depends on the patient himself; the same cultural factors that interfere with the seeking of care also interfere with its continuity. Their lack of identification with a central figure and the inflexibility of the depersonalized system of care are key problems that must be solved before adequate continuity of care can be established. Under present circumstances it is not surprising that these patients often do not comply with medical advice.

COMPLETENESS

Completeness is an essential facet of comprehensive medical care. However, certain segments of completeness are markedly inadequate in current medical practices. This is particularly true in the area of preventive services such as health promotion, disease prevention and efforts at early diagnosis.

Although these areas are not very well developed for even the affluent population, they are practically non-existent for the poor. In fact, there are systematic barriers to preventive services, built into the structure of many welfare services.

During the current century the focus of medical interest, funds, energy and research has been on disability limitation (i.e., conventional acute and chronic care). The poverty group has shared in the fruits of these activities but not nearly to the extent of the non-poverty group, as demonstrated by the excess mortality from influenza and pneumonia noted in this group. Knowledge and resources in rehabilitation are one of the relatively new and developing areas of medicine, and, as one would expect, application of the assets of this field to the community generally has lagged behind conventional care, but the lag is especially glaring for the poverty group.

RECOMMENDATIONS

Having obtained the above data, specific recommendations for developing programs that would change the patterns of medical care and potentially alter the unfavorable morbidity and mortality statistics were made. Two approaches were proposed. First in order to change the total pattern of care it was recommended that there be developed a long term medical care system which will make it possible to deliver comprehensive care to a whole community. The manpower facilities do not currently exist which might enable us to guarantee to every resident of our city a personal physician. However, by the joint effort of the major community hospitals, teaching institutions and voluntary agencies there can develop a series of comprehensive family care centers and coordinated programs of health care in defined geographic areas. These centers, planned and administered by existing voluntary hospitals and medical schools, would extend the services of these institutions into the community. The Board of Health would

work with hospitals and medical schools in defining areas, coordinating the programs, and interdigitating the services currently available at Board of Health stations in these communities with the new programs to be developed. Implicit in the development of these centers would be the experimentation with new methods for using medical and ancillary personnel as well as learning new ways to deal with the socio-economic and cultural factors which discourage the use of medical facilities by the poor.

Briefly, the plan invisages three echelons of care. The first echelon is represented by the public health nurse and aides trained to assist her, who would serve in the role of a family health advisor overcoming some of the problems encountered in initiation and continuity of care. The second echelon is the Neighborhood Health Center. Each Neighborhood Health Center would be operated by a parent institution as an extension of their outpatient services into the community. The parent institution would then serve as the third echelon of care, providing referral outpatient services and in-patient hospital care when needed. By utilizing the resources of the major teaching hospitals, community hospitals and medical schools it is hoped that the admitted short supply of medical facilities can be utilized more effectively, and that specific problems in coordination and continuity of medical care can be overcome. However, this approach has distinct shortcomings when one views the size of the population to be served, probably well over a million persons in Chicago. The specific statistics reveal urgent and acute medical needs. One cannot afford to wait for these programs to unfold and develop a significant impact on city wide mortality or morbidity figures. Therefore, the study group further recommended that immediate specific goals be set for large scale, city wide programs. In selecting these programs, both the areas of greatest need and the feasibility of successfully carrying out the programs on a broad base were considered. These programs include among others, the pre-school examination, prenatal care, immunization, health education and extension of family planning services. These crash programs can develop as extensions of programs currently in operation. The fragmentation and lack of coordination inherent in present programs which have arisen piecemeal in the past must disappear and the programs merged into an acceptable, coordinated whole. □

SUMMARY

A study of health care in Chicago's poverty communities revealed striking differences in levels of health and patterns of medical care. The development of comprehensive family care centers was recommended in an effort to deal with some of the problems that were identified. □

ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

Deinhardt, F.: Rous Sarcoma Virus: Induction of Neoplasms in New World Nonhuman Primates. *Nature, 210:5034, 433, April 23, 1966.*

In the last four years this laboratory has characterized and evaluated marmosets for their suitability in tumor virus research. Marmosets may be kept and bred under standard laboratory conditions. Five of the marmosets born in captivity were inoculated subcutaneously and intramuscularly during the first twenty-four hours of life with cell free preparations of Rous Sarcoma virus—Schmidt-Ruppin strain. All developed invasive, metastasizing, immature sarcomas between 20 to 90 days after inoculation and died from their malignant disease between 35 to 117 days. Live tumor cells from one of these animals were inoculated into its twin at the age of 39 days and this animal developed a large sarcoma at the inoculation site within 2 weeks.

Complete autopsies with conventional and electron microscopical histology were performed on all animals. Tumors and various organs were viably preserved in liquid nitrogen. Tissues were grown out in culture. The original outgrowth in tissue culture and cells after several tissue culture passages of both tumors and normal tissues were karyotyped. The chromosomes were clearly identifiable as marmoset chromosomes. A number of inconsistent chromosomal aberrations were observed in the tumor cells without the appearance of specific markers. The results of current studies on the antigenic analysis of the tumor cells, and the presence or absence of virus in the tumors and other tissues will be discussed.

McCreary, P.; Battifora, H.A.; Laing, G. H.; and Hass, G. M.: Protective Effect of Magnesium Deficiency on Experimental Allergic Encephalomyelitis in the Rat. *Proc. Soc. Exp. Biol. Med., 121:1130-1133, 1966.*

Acutely magnesium deficient rats exhibit hyperemia of the skin, leukocytosis, eosinophilia, degranulation of mast cells and histaminuria. These changes are preventable with antihistaminic therapy. The histological lesions of more prolonged magnesium deficiency bear a resemblance to those of delayed hypersensitivity. Because of the suggestion of a hyperimmune state in magnesium deficiency, an attempt to produce experimental allergic encephalomyelitis (EAE) in magnesium deficient rats was made. The results show that, rather than enhancing the development of EAE, magnesium deficiency exerts a protective effect. Histological evidence of EAE occurred in 70% of control rats fed normal diets and in only 18% of rats started on a magnesium deficient diet at various intervals before and after injection of the encephalitogenic mixture. Furthermore, the degree of EAE in magnesium deficient rats was inversely proportional to the severity of the myopathy characteristic of magnesium deficiency. The reason for the resistance of the magnesium deficient animal to EAE remains obscure.

Bogdonoff, M. L.: The Radiologic Anatomy and Physiology of Lung Embolus and Infarction. *Radiology, 87:16-22, July 1966.*

The radiologic and physiologic findings in 44 dogs subjected to pulmonary embolus, hemorrhagic pneumonitis, or pulmonary arterial occlusive banding have been obtained. Contrast visualization of the bronchi, pulmonary arteries and pulmonary veins have been serially recorded.

1. There is no radiographic evidence of spasm of bronchi to the fifth order following lodgment of Ivalon or autologous clot pulmonary emboli in the anesthetized dog.
2. Previously documented changes of tachypnea, drop in tidal volume and moderate rise in mean arterial pressure accompanied by arterial oxygen desaturation have all been confirmed in animals when approximately one-half of the arteriographically determined

blood supply was occluded by artificial embolus.
3. Infarction is an uncommon event following lodgment of Ivalon sponge emboli in the dog (it occurs in about 20% of animals).
4. Evidence suggesting the probability of venous stasis or spasm in the pathogenesis of hemorrhagic lung infarction in the dog has been cited.
5. The Ivalon sponge embolus method is unpredictable, but sometimes is useful in producing a lesion mimicking lung infarction. There are obvious differences between the experimental models employed here and the human lesion of hemorrhagic lung infarct.

Levin, H. J.; Beattie, E. J., Jr.; and Economou, S. G.: The Influence of Neonatal Thymectomy and Neonatal Thymectomy with Splenectomy on Renal Homograft Acceptance in Puppies. *Invest. Urol., 3:5, 479, September 1965.*

This study attempted to determine the effect of thymectomy and thymectomy with splenectomy on renal homograft acceptance in puppies as compared to controls having no previous surgery. It was found that there was no significant difference in duration of acceptance among the above three groups.

Apter, J.T.; Rabinowitz, M.; and Cummings, D. H.: Correlation of Visco-elastic Properties of Large Arteries with Microscopic Structure. *Circ. Res., 19:104-121, July 1966.*

The media of 14 regions of the aorta and 3 regions of the pulmonary artery of dogs were subjected to a step-function circumferential stretch taking 20 msec to complete. The tension rose synchronously with the increase in circumference, then dropped exponentially to a reasonably steady state within 2 sec. A mathematical model, developed consistent with this stress-relaxation curve, showed how to use the tension curves to measure a viscous, a series-elastic, and a parallel-elastic constant unique for a given curve. These constants were compared with the microscopic structure of the same or similar segments; collagen was determined as hydroxyproline in a water soluble fraction, elastin as hydroxyproline in the residue and from the width and number of elastic lamellae, and muscle from the nitrogen content of a non-fibrous fraction, from cell counts and from contractility. The constituents varied widely and independently enough to permit correlating viscous and elastic constants with microscopic structure. The viscous and series-elastic constants were higher where muscle content was high, and increased markedly when the muscle was tonically contracted. The parallel-elastic constant was high when elastin was high and in the presence of contracted muscle, but seemed independent of collagen content, at the moderate tensions tested.

Friedberg, S. A.: Recent Trends in Surgery of the Larynx. *Surg. Clinc. of N. Amer., 46:99-109, Feb. 1966.*

Certain types of vocal cord paralysis are characterized by inadequate glottic closure with air wastage and poor voice function. These can now be corrected by the intracordal injection of Teflon which augments the cord mass on the involved side, thus increasing the competency of the glottic sphincter.

Appreciation of the variations in lymphatic drainage of different areas of the larynx has led to significant modifications in laryngeal cancer surgery. It is now possible to conserve both voice and swallowing functions by extirpative procedures which remove certain selected primary lesions in continuity with nodal sites of actual or potential lymphatic spread. The results have been shown to compare favorably with those previously obtained by sacrifice of the entire larynx.

Extensive laryngeal neoplastic lesions have long posed difficult problems in management. Efforts towards improving the salvage rate in such cases are currently based upon a combination of preoperative radiation and surgery. Results at this time indicate that control of extensive disease under this regime represents an improvement over previous forms of therapy.

One of the problems associated with automobile accidents has been the failure to recognize injuries to the larynx when concern for face, chest or abdominal trauma diverts the

attention of the examining physician. It is important to institute definitive therapy promptly to avoid subsequent scarring and stenosis. Both external and internal approaches are available to the laryngologist in acute injuries. Early recognition holds the key to successful management and this involves suspicion or awareness of the condition.

Davis, C. B., Jr.; Fell, E. H.; and Taylor, C. B.: Postoperative Aneurysm Following Surgery for Coarctation of Aorta. *Sug. Gynec. Obstet., 121:1043-48, November 1965.*

The first successful resection of a coarctation of the thoracic aorta was performed by Crafoord of Stockholm in 1944. Since then, the surgical management of this vascular anomaly has become well established. An infrequent complication of this type of surgery is the occurrence of a postoperative aneurysm of the aorta at or near the site of the anastomosis. Although only a few such instances have been reported in the surgical literature, we have encountered 3 patients with coarctation of the thoracic aorta, in whom within 1 year after the initial surgical repair, a false aneurysm was found in the region of the primary end to end anastomosis.

The clinical features and management of these 3 patients are presented in addition to a review of individual cases reported by other vascular surgeons. Although all of these patients were reoperated upon, in only 2 was resection of the aneurysm possible. Mortality occurred in 2 patients.

The exact mechanism responsible for the development of this aneurysm is not well established. Numerous etiologic factors have been suggested. 1) The integrity of the arterial wall must be considered in relation to the degree of poststenotic dilatation or the extent of associated atherosclerosis. 2) Any degree of injury to the aortic wall due to cross clamping may be significant. 3) Improperly placed sutures and the type of suture material employed may be factors. 4) Infection of sutures and postoperative bacterial endarteritis may be significant.

It is suggested that an awareness of the possible development of this complication should result in early recognition and prompt surgical intervention in order to avoid fatal rupture of the aneurysm. Because infection was significant in 2 of the 3 patients, it is recommended that any obvious bacterial infection must be vigorously treated and eliminated prior to surgical intervention.

de Takats, G.: Frostbite. *Pres. St. Luke's Hosp. Med. Bull., 5:1, 12-18, January 1966.*

One would think that the prevention and treatment of cold injuries must be as old as any medical endeavor, and truly there is nothing new under the sun. Nevertheless, there are recurrent fads and fancies. In this brief report, emphasis has been placed on; 1) rapid rewarming; 2) early sympathetic blocks; 3) dry dressings with avoidance of tight bandaging and ointments; 4) spontaneous demarcation of necrotic tissue, and; 5) late sympathectomies in case of sympathetic hyperactivity.

Naturally, prevention is more important, and hunters, skiers, explorers, mountain climbers and outdoor workers need careful indoctrination. As long as there are wars, and unless the characteristics of war change to atomic or germ warfare, men will be injured, immobilized and exposed in cold climates. The experience of the Korean war would indicate that large masses of the fighting force still suffer cold injuries.

de Takats, G.: Diabetic Vascular Disease. *Amer. Surg., 32:355-64, June 1966.*

The faulty carbohydrate and fat metabolism of the diabetic, the diffuse major and terminal vascular disease which involves the cerebral, cardiac, renal and mesenteric arteries all need intensive study before any type of management can be outlined. In this survey, the important role of microangiopathy and neuropathy has been stressed, each of which make diabetic vascular disease a special entity. The slow healing of wounds, the tendency to necrosis and the poor defensive response to infection can be explained readily by the additional factors which do not operate in the non-diabetic. The early recognition of the prediabetic and latent diabetic may hopefully prevent or reverse this mysterious deposit in the small vessels. Electron microscopy and fluorescence microscopy are potent tools in present and future studies.

ESBYTERIAN-ST. LUKE'S HOSPITAL MEDICAL BULLETIN